NEURO-PSYCHIATRIC ILLNESS, BRAIN INJURY, NEUROTOXIC DRUGS AND MORAL INJURY IN AUSTRALIAN DEFENCE FORCE VETERANS

Submission to the Senate Foreign Affairs, Defence and Trade References Committee Inquiry into the Mental Health of Australian Defence Force Serving Personnel

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July 2015

"Mefloquine may induce psychiatric symptoms such as anxiety disorders, paranoia, depression, hallucinations and psychosis. Psychiatric symptoms such as abnormal dreams/nightmares, acute anxiety, depression, restlessness or confusion have to be regarded as prodromal for a more serious event. Cases of suicide, suicidal thoughts and self-endangering behaviour such as attempted suicide have been reported."

Roche Products, *Summary of Product Characteristics*, 24 December 2014

"It is Defence's assessment that [an outreach program for mefloquine veterans] would cause unnecessary distress to the vast majority of recipients. This distress outweighs any potential benefit to the potentially very small number of members with unrecognised long-term or permanent side-effects."

Stuart Robert (Assistant Minister for Defence), 1 April 2015

Introduction

This is a submission to the Senate Foreign Affairs, Defence and Trade References Committee Inquiry into the Mental Health of Australian Defence Force Serving Personnel.

I have been a serving officer in the Australian Army for the past 26 years. My career has included operational deployments to Bougainville (1999), Ethiopia & Eritrea (2001), Sumatra (2005), Iraq (2006) and Afghanistan (2011-12 and 2013). I have extensive experience in dealing with mental illness among colleagues and subordinates, including the available support services, as well as first-hand experience in seeking support from those same organisations for myself and my family.

Given the Committee's focus on the adequacy of support, evaluation and counselling services, rather than individual cases of mental illness, the purpose of this submission is to highlight institutional failings in numerous organisations that are preventing veterans and their families from receiving effective support, specifically those affected by neuro-psychiatric illnesses resulting from physical trauma (traumatic brain injury or TBI), neuro-psychiatric effects of neurotoxic drugs such as mefloquine (trade name Lariam) and related psychological distress. In order to highlight these failings, however, it is necessary to draw on the experience of individual cases.

To its credit, both the Australian Defence Force (ADF) and Department of Veterans Affairs (DVA) have made significant improvements in recent years in supporting veterans experiencing mental health problems such as PTSD. These include efforts to reduce the stigma surrounding mental health and psychiatric treatments for PTSD. Unfortunately, PTSD/anxiety/depression has become a "diagnosis of convenience" which not only prevents those veterans with more complex neuro-psychiatric illnesses caused by TBI and/or neurotoxic drugs from receiving proper care and support, but exacerbates their illnesses and in some cases leaves them and their families alienated from adequate support. There is an over-simplistic focus among policy makers and medical staff on exposure to traumatic events during deployments resulting in PTSD, while many veterans with more complex illnesses with more complex causes are being misdiagnosed, mistreated, and/or failing to receive proper care.

Specifically in relation to the neuro-psychiatric effects of mefloquine, my efforts in seeking to implement an outreach program to assist affected veterans has encountered a culture of denial, deceit and impunity that extends to the most senior officers in the ADF, the Assistant Minister for Defence and senior officials in several other organisations, that not only contravenes the mental health and related policies of those organisations but is a manifest breach of their duty of care under the relevant legislation.

Another important contextual aspect of veterans' mental health that I would like to draw to the Committee's attention is the concept of *moral injury*, which goes beyond the pathologisation of mental illness to better explain both the causes of veterans' trauma and the social isolation they continue to experience in the absence of proper recognition and care. This will be explained below. Suffice to say that what needs to be understood from the outset of this submission is that the culture of denial, deceit and impunity currently evident in the institutions which have a role in veterans mental health needs to be addressed comprehensively. Unless this is done, many veterans will continue to experience social isolation as well as alienation from the support they need.

Neuro-psychiatric Illness

While acknowledging the Committee's terms of reference and focus on mental health, I believe that one of the problems preventing veterans from receiving proper care is a narrow, over-emphasis on *psychology*, when many injuries and illnesses experienced by veterans are more complex, necessitating a broader approach that includes *psychiatry*, *neurology* and the relationships between those fields. Although I have no qualifications in medical or related sciences, my experiences in dealing with medical and mental health in the ADF have led me to believe that a more holistic approach is required.

Psychology is the study of mind and behaviour, which attempts to understand the role of mental functions in individual and social behaviour. Psychiatry is the medical specialty devoted to the study, diagnosis, treatment, and prevention of mental disorders, while Neurology disorders of the nervous system. Neuro-psychiatry is the branch of medicine that deals with mental disorders attributable to diseases of the nervous system. Interestingly, neuro-psychiatry actually preceded psychiatry and neurology however those fields subsequently split and are usually practiced separately, with neuro-psychiatry now a sub-specialty of psychiatry.

ADF personnel face numerous threats to their health while deployed on operations. In recent decades increasing emphasis has been placed on psychological stress, including exposure to traumatic events which can cause PTSD, or more general, prolonged stress which can cause depression, anxiety or other psychiatric illnesses. Obviously, physical threats such as projectiles and blast can cause physical trauma, however there has been a growing awareness of physical injuries as causes of neurological damage, with symptoms including cognitive impairment, for example blast causing TBI. Other causes of neurological damage can include exposure to neurotoxins, either as environmental chemicals or neurotoxic drugs. Advances in neurological science in *treatment* and rehabilitation for physical injuries have been prominent, however insufficient emphasis is given to neurology as a causative factor.

Despite these advances, many veterans experience problems in seeking appropriate diagnosis, treatment and support for more complex neuro-psychiatric injuries or illnesses due to a reluctance by medical practitioners to investigate neurological causes for ostensibly "psychiatric" or "psychological" problems. Neurological symptoms are often initially dismissed as "psychological". One example recently reported in the media was ADF veteran Matt Millhouse, who sustained TBI from an IED blast while deployed in Iraq in 2004. Although he experienced concussion at the time, he returned to full duty without any obvious long term injury. Years later he sought treatment for psychological symptoms and was initially diagnosed with PTSD and depression. Subsequent medical investigation determined that he had actually developed incurable, early-onset dementia, caused by the TBI.[1]

Given the variety and complexity of health threats encountered by ADF personnel deployed on operations, many of the resulting injuries or illnesses would best be re-conceived more holistically as neuro-psychiatric rather than "mental health" problems, in order to provide more effective investigation, diagnosis, treatment and support. These include, but are not limited to, what have been described as "signature injuries of modern war" such as PTSD, TBI and mefloquine toxicity.

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[1] Steven Burling (Producer), "After the Blast", Sixty Minutes, Channel Nine Television, broadcast 21 June 2015, at http://www.9jumpin.com.au/show/60minutes/stories/2015/june/after-the-blast/.

Mefloquine and its Neuro-psychiatric Side Effects

Mefloquine hydrochloride (trade name *Lariam*) is a quinoline-derived anti-malarial drug that has been widely used by military forces, including the ADF, for the last quarter of a century. The neurotoxic properties of the drug and its neuro-psychiatric side effects have long been acknowledged by manufacturers and health authorities including the Surgeon General ADF (SGADF), however conventional wisdom has been that these side effects are only temporary, and only experienced by individuals with pre-existing psychiatric illness. However recent scientific-medical research now indicates that the neuro-pshychiatric side effects can be long term or permanent because the drug can cause lasting injury to the brainstem and emotional centres in the limbic system (Attachment 1). Significantly, authorities such as the US Centres for Disease Control (CDC) have warned that mefloquine's side effects can confound the diagnosis of PTSD and TBI among veterans because they are similar to the symptoms of those illnesses.

There is an extensive body of published research dating back as far as the 1970s providing evidence than quinolones including mefloquine can cause brain injuries that result in these neuro-psychiatric symptoms. Despite this, mefloquine was approved by drug regulators in America, Europe and the Australian Therepeutic Goods Administration (TGA), in the absence of the necessary pre-licensing research. Senior military medical officers have criticised this regulatory failure, which might otherwise have prevented widespread harm caused by mefloquine's adverse side effects (Attachment 2).

Another aspect of conventional wisdom regarding mefloquine is that its more serious neuro-phsychiatric side effects are only experienced by very small numbers of individuals. This is now discredited in published medical-scientific research. In one civilian study alone, 28 percent of participants experienced side effects considered to be prodromal to lasting brain injury. In another example, the UK Ministry of Defence revealed this year that, of 17,000 military personnel administered mefloquine since 2008, 994 (six percent) subsequently required psychiatric treatment.[2]

Mefloquine in the ADF

Mefloquine has been in use in the ADF since 1990, administered to personnel on major deployments including Somalia, Cambodia, Bougainville, East Timor, Solomon Islands, Iraq and Afghanistan, as well as many other smaller operational and training deployments to malarious areas. Given the size and/or duration of those operations and intolerability of alternatives such as doxycycline, a reasonable estimate of the number of ADF veterans who have had significant exposure to mefloquine neurotoxicity would be at least several thousand, possibly much higher (Attachment 3), although exact figures are not publicly available. Given this exposure it is likely that hundreds of ADF veterans have experienced long-term or permanent neuro-psychiatric side effects. Many of these will have been misdiagnosed and few if any will have received proper care or support. Some of them have possibly suicided, either as a direct result of mefloquine use or an indirect result of inadequate care.

In 2001-02, 1,157 ADF personnel were administered mefloquine during drug trials by the Army Malaria Institute (AMI) in East Timor. Following these trials there were numerous

[2] Jonathan Owen, "Lariam: Hundreds of British soldiers suffering from mental illness after being given anti-malarial drug", *The Independent*, 15 April 2015, at http://www.independent.co.uk/life-style/health-and-families/health-news/lariam-hundreds-of-british-soldiers-suffering-from-mental-illness-after-being-given-antimalarial-drug-10179792.html.

media reports that participants had experienced paranoia, suicide ideation and other psychotic side effects. One soldier was reported to have taken his girlfriend hostage at gunpoint soon after his return from East Timor. The experiences of these participants are consistent with mefloquine's accepted neuro-psychiatric side effects. Despite ADF claims to the contrary, involvement of soldiers in these trials was manifestly unethical. Participants were not properly informed of the drug's toxic effects and the Commanding Officer of at least one of the units involved (who is now a Lieutenant General) directed that any of his subordinates who did not "volunteer" to participate in the trial would be excluded from the deployment. In effect they were ordered to take a drug that exposed them to permanent neurotoxic brain injury.

Mefloquine in the International Military Context

Regardless of the specific numbers of ADF personnel administered mefloquine, the 2001-02 drug trials by AMI are also significant in the international military context. Soon after entering the civilian market in the early 1990s mefloquine became notorious for its neuro-psychiatric side effects, falling out of favour to the extent that its manufacturer, Roche, reportedly wanted to withdraw it from the market altogether. According to at least one senior US military official, they were influenced to continue marketing the drug because the US military feared there were so few alternative anti-malarials available. Mefloquine has since been used by many hunderds of thousands of US, UK and Canadian military personnel, among other nationalities. The AMI trial results gave policy makers from those countries false assurances of mefloquine's safety and tolerability.

Recently, however, as the evidence of mefloquine's neurotoxic side effects has mounted, some international military authorities have begun to make coordinated efforts to care for affected veterans. Shortly after the US Food and Drug Administration mandated its most stringent "black box" warning regarding mefloquine's long-term or permanent neuro-psychiatric side effects in 2013, the commander of US Army Special Operations Command, an organisation equivalent in size to the Australian Army, ordered that mefloquine no longer be used "due to risk of serious psychiatric and nerve side effects" and those exhibiting symptoms of toxicity undergo thorough medical assessment (Attachment 4). More recently, the US Department of Veterans Affairs has listed the drug on its publicly available "deployment exposures" information resources and commenced an intake program specifically for mefloquine veterans.

Institutional Barriers to Effective Support for Mefloquine Veterans

Despite published medical-scientific research of mefloquine's long-term or permanent neuro-psychiatric side effects, warnings from the manufacturer and drug regulators and specific advice that mefloquine can confound diagnosis of PTSD and TBI among veterans, there are a number of institutional barriers preventing mefloquine veterans from receiving proper care. The observations summarised here reflect my recent personal experiences with the ADF health system and civilian health specialists.

As I mentioned in the introduction above, there have been significant improvements reducing the stigma of mental illness and providing support for veterans who seek treatment for PTSD and psychiatric illnesses. The downside of this, however, is a tendency to diagnose and treat veterans with PTSD, depression, anxiety or other purely psychiatric conditions without thorough investigation of other neurological causes such as TBI or neurotoxic drugs. These "diagnoses of convenience" can result in psychiatric drug treatments or psychological therapy

that is ineffective and/or unnecessarily delays more comprehensive investigation and rehabilitation.

Specifically in relation to mefloquine, there are medical professionals who exhibit blind faith in regulatory agencies such as the TGA. I was personally advised by one experienced doctor that there should be no concern regarding mefloquine "because it's approved by the TGA". This doctor was blissfully unaware that the drug was approved by the TGA in the absence of Phase III clinical trials. Further, numerous medical professionals including reputable neurologists are simply unaware of the recent published research showing that mefloquine is a neurotoxic drug that can cause long-term or permanent side-effects, confounding diagnosis of PTSD and TBI. Even when presented with this published research, they can simply remain dismissive.

Finally, ADF health officials believe that existing *psychological* screening procedures are adequate to ensure veterans with mefloquine toxicity will be identified and treated. Despite the fact that mefloquine is known to be neurotoxic, despite manufacturer's warnings that relatively minor side effects may be prodromal for more serious events including suicide, despite the fact that mefloquine is a prescription drug recorded in the ADF's electronic pharmaceutical database, there is *no screening for current or former ADF personnel who have taken mefloquine*. In my own case, despite providing my GP with the recent research on mefloquine after reporting symptoms consistent with manufacturer's warnings, it took more than 12 months of repeated requests to be referred to a neurologist, during which time I was counselled for "anger issues" and threatened with disciplinary action. Existing procedures *cannot* be expected to identify veterans experiencing long-term or permanent mefloquine toxicity.

These institutional barriers necessitate a dedicated outreach program to ensure that mefloquine veterans and their families receive the appropriate care and support.

Proposed Outreach Program and (Lack of) Responses by Commonwealth Agencies

Having discovered the recently published research in early 2014, I drafted a paper on mefloquine neurotoxicity and veterans' mental health (Attachment 3), including a proposed outreach program, consistent with various ADF and DVA "evidence based" health policies and the Commonwealth's legal duty of care under the *Commonwealth Work Health and Safety (WHS) Act 2011*. The paper has been acknowledged by senior ADF medical officers, senior ADF leadership and the Assistant Minister for Defence. However no discernible action has been taken other than threatening me with disciplinary action.

Perversely, senior ADF officials have relied on advice from AMI and other medical officers involved in the 2001-02 AMI mefloquine trials in deciding to take no action. This obvious conflict of interest has resulted in the culture of denial, deceit and impunity that I mention in the above introduction. Correspondence from senior ADF leaders and the Assistant Minister for Defence simply repeats misinformation and flawed arguments based on outdated research, to justify their inaction. The policy enunciated by the Assistant Minister in the above quote, i.e. that Defence is unwilling to properly care for veterans with serious illness resulting from their ADF service on the basis that doing so "would cause unnecessary distress" to unaffected personnel, is quite simply indefensible, legally or morally. This steadfast refusal to act on the evidence indicates that a successful outreach program would need to be implemented by an independent agency.

In addition to proposing the outreach program to Defence officials, in early 2014 I forwarded my paper and other related research to Comcare, requesting that they investigate breaches of the WHS Act. Approximately six months later I was advised that Comcare intended to take no action. In early 2015 I provided further evidence to Comcare and requested that they investigate breaches of the WHS Act relating to Defence's failure in its duty of care. No discernible action has been taken.

Moral Injury

With the above institutional failings in mind, it's important for the Committee to understand the concept of moral injury, which was developed by psychiatrist Jonathan Shay in the 1990s while he worked for the US Department of Veterans Affairs treating Vietnam veterans with PTSD and has been the subject of further research by various academics in recent years.

One of Shay's early observations about the pathologisation of PTSD, now widely accepted by policy-makers, was that the condition is better described as an *injury* rather than an *illness*. Although PTSD and moral injury are frequently co-morbid, Shay has observed that moral injury is distinct because it injures veterans' *moral character*, destroying their capacity for *social trust*, where social trust is "the expectation that power will be used in accordance with 'what's right.'" He defines moral injury as follows:

> *"Moral injury is present when (1) there has been a betrayal of what is morally correct; (2) by someone who holds legitimate authority; and (3) in a high-stakes situation."*[3]

Notably, Shay's factor (2) above is an instance of what he calls "leadership malpractice".

Recent research across a variety of disciplines now acknowledges that a narrow "mental illness" medical diagnosis of "PTSD" often precludes proper understanding of, and effective responses to, the chronic despair, anger and alienation experienced by many returning veterans. While there are now good avenues for treatment and management of PTSD, these cannot address the debilitating social problems for veterans and their families caused by moral injury. These problems include suicidality, interpersonal violence, substance abuse, family breakdown, social isolation, unemployment and homelessness. Shay makes this point explicitly:

> *"Because their psychological injuries have destroyed social trust, the most severely injured veterans are least able to get and retain access to treatment. [Moral injury] destroys the key resource - trust - necessary for its successful treatment. So we have a paradox, or at least an impasse. The very thing that constitutes the difference between [PTSD] and [moral injury] - destruction of social trust - blocks the treatment of [moral Injury].*
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> *"The veterans have reason, based on their experience, to distrust credentials, institutional position, and abstract, universally applied procedures. These veterans have had the very real experience of lives lost and people maimed when a person in a*

[3] "Casualties", *Daedalus*, Summer 2011, Vol. 140, No. 3, pp. 179-188, at http://www.mitpressjournals.org/doi/abs/10.1162/DAED_a_00107#.VZ5UeM4w_IU.

> *position of power "went by the book," rather than first looking sharply at the particulars, and then applying the book to them with flexibility and good sense."*[4]

Given the preceding contents of this submission, the significance of moral injury should now be clear, particularly the *lack of trust* experienced by veterans as a result of their ADF service. Actions by authorities that destroy trust either during or subsequent to operational service can be a *cause* of psychological injuries. Lack of trust can be a key *symptom* of neuro-psychiatric illnesses, including those caused by TBI and neurotoxic drugs such as mefloquine. And lack of trust can be a major barrier that *prevents* veterans receiving effective care.

Efforts by various agencies to "destigmatise" mental illness in order to encourage those affected to seek help, however laudable, will likely be ineffective if the intended recipients don't trust the organisations intending to provide help. The respective organisations need to be demonstrably *trustworthy*. The culture of denial, deceit and impunity that I have described above epitomises an organisation that is demonstrably *untrustworthy*. Until that negative culture is properly addressed, many veterans experiencing neuropsychiatric illness and/or moral injury will not be properly rehabilitated and will continue to experience the numerous problems that result from a lack of social trust. Indeed the behaviour of these institutions continues to be a key *cause* of the very injury that is preventing many veterans from being effectively rehabilitated for their ostensible "mental health" problems.

Conclusion and Recommendations

I am grateful for the opportunity to contribute to this Inquiry. While there have been significant improvements in the provision of mental health support for ADF veterans in recent years, there are significant institutional problems that are preventing those with more complex neuro-psychiatric illnesses from receiving proper support. Generally speaking, the current approach to "mental health" focuses to narrowly on psychology and psychiatry. This needs to be broadened to more holistic approach that incorporates an emphasis on neuro-psychiatric illness, in order to better address the complex health threats encountered by contemporary veterans. More specifically in relation to the thousands of ADF veterans exposed to the neurotoxic drug mefloquine, the Commonwealth should implement a comprehensive outreach program to properly care for those experiencing the long-term or permanent neuro-psychiatric side effects, many of whom have likely been misdiagnosed, mistreated, or otherwise failed to receive proper care. Given that the ADF refuses to do so, this task needs to be given to an independent agency. An important aspect of this program would be to address the current negative culture and restore necessary trust in those organisations responsible for veterans' health care.

In order to address the matters raised in this submission I recommend that the Commonwealth:

- Conduct a full, independent review of the existing ADF and DVA health policies, procedures and practices for veterans with neuro-psychiatric illnesses and/or symptoms, brain injuries, exposure to neurotoxic drugs including (but not limited to mefloquine), including investigation, treatment and support, in order to provide improved care for those veterans and their families.

[4] *Odysseus in America: Combat Trauma and the Trials of Homecoming*, Scribner, Sydney, 2002, p. 166.

- Direct an independent body to implement the proposed mefloquine veterans outreach program, including the identification of all personnel administered mefloquine during their service, research, awareness and education, training health staff, diagnosis, treatment, rehabilitation and social support for veterans and their families. The implementing body would be independent of the ADF and DVA, with the relevant powers to direct those organisations to achieve the appropriate outcomes.

- Conduct a full, independent inquiry into mefloquine use in the ADF and its impact on veterans and their families, including the conduct of clinical trials by the AMI, the involvement of the manufacturer, decisions by senior ADF leadership and the involvement of foreign governments and organisations.

- Prohibit, by law, the conduct of clinical trials involving participation by ADF personnel deployed on operations.

- Investigate the failure by Comcare to enforce the appropriate provisions of the WHS Act relating to mefloquine use in the ADF.

Attachments

1. Remington L. Nevin, *Idiosyncratic Quinoline Central Nervous System Toxicity*, 2014

2. Ashley M. Croft, *A Lesson Learnt: The Rise and Fall of Lariam and Halfan*, 2007

3. Stuart McCarthy, *Mefloquine Neurotoxicity, Commonwealth Duty of Care and Veterans' Mental Health: A Case for Proactive Outreach*, 2015

4. US Army Special Operations Command, Ceasing Use of Mefloquine in US Army Special Operations Command Units, 2013

International Journal for Parasitology: Drugs and Drug Resistance 4 (2014) 118–125

Contents lists available at ScienceDirect

International Journal for Parasitology: Drugs and Drug Resistance

journal homepage: www.elsevier.com/locate/ijpddr

Current Opinion

Idiosyncratic quinoline central nervous system toxicity: Historical insights into the chronic neurological sequelae of mefloquine ☆

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ARTICLE INFO

Article history:
Received 3 February 2014
Received in revised form 17 March 2014
Accepted 19 March 2014
Available online 5 April 2014

Keywords:
Mefloquine
Quinoline
Neurotoxicity
Adverse effects
Malaria
Schistosomiasis

ABSTRACT

Mefloquine is a quinoline derivative antimalarial which demonstrates promise for the treatment of schistosomiasis. Traditionally employed in prophylaxis and treatment of chloroquine-resistant *Plasmodium falciparum* malaria, recent changes to the approved European and U.S. product labeling for mefloquine now warn of a risk of permanent and irreversible neurological sequelae including vertigo, loss of balance and symptoms of polyneuropathy. The newly described permanent nature of certain of these neurological effects challenges the conventional belief that they are due merely to the long half-life of mefloquine and its continued presence in the body, and raises new considerations for the rational use of the drug against parasitic disease. In this opinion, it is proposed that many of the reported lasting adverse neurological effects of mefloquine are consistent with the chronic sequelae of a well characterized but idiosyncratic central nervous system (CNS) toxicity syndrome (or toxidrome) common to certain historical antimalarial and antiparasitic quinolines and associated with a risk of permanent neuronal degeneration within specific CNS regions including the brainstem. Issues in the development and licensing of mefloquine are then considered in the context of historical awareness of the idiosyncratic CNS toxicity of related quinoline drugs. It is anticipated that the information presented in this opinion will aid in the future clinical recognition of the mefloquine toxidrome and its chronic sequelae, and in informing improved regulatory evaluation of mefloquine and related quinoline drugs as they are explored for expanded antiparasitic use and for other indications.

1. Introduction

Mefloquine is a 4-quinolinemethanol antimalarial and antiparasitic drug that is structurally related to quinine. Although increasingly investigated for its promising antischistosomal properties (Keiser et al., 2010; Basra et al., 2013), mefloquine is associated with a diverse range of adverse neurological effects (Croft, 2007a) which, together with the drug's neuropsychiatric contraindications (Wooltorton, 2002), have limited the drug's utility for its original antimalarial indications, particularly for prevention of disease (Arznei-Telegramm, 2013b; Bisoffi et al., 2013).

According to recent European product labeling (Hoffmann-La Roche, 2013a) and the results of a randomized blinded trial (Overbosch et al., 2001), commonly reported neurological effects from mefloquine which occur in 1–10% of prophylactic users include vertigo and visual difficulties. Additional idiosyncratic neurological effects reported in both European and U.S. product labeling include balance disorder, peripheral neuropathy, paresthesias, tremor, and ataxia (Hoffmann-La Roche, 2013b, 2014; Roxanne Laboratories, 2013). Case reports also describe dysesthesias (Félix et al., 1985; Jha et al., 2006), disequilibrium (Patchen et al., 1989), nystagmus (Nevin, 2012a), and photophobia (Caillon et al., 1992).

Although adverse neurological effects had previously been considered fully reversible (Arznei-Telegramm, 2013a), diminishing in intensity with the slow elimination of the drug (Nevin, 2013), in 2012, the U.S. Food and Drug Administration (FDA) announced it was reevaluating mefloquine specifically for concerns of an association with lasting vestibular disorder based on new signals detected from its FDA Adverse Event Reporting System (FAERS) (U.S. Food and Drug Administration, 2012). In 2013, European regulators updated the drug's core safety profile to warn that symptoms of polyneuropathy developing during mefloquine use were associated with risk of an irreversible neurological condition (Bundesinstitut für Arzneimittel und Medizinprodukte, 2013), and FDA updated the U.S. product labeling with a boxed warning that

☆ *Funding statement*: Publication of this article was funded in part by the Open Access Promotion Fund of the Johns Hopkins University Libraries. No additional external funding was received for this study.
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http://dx.doi.org/10.1016/j.ijpddr.2014.03.002
2211-3207/

other neurological effects including vertigo and loss of balance could be permanent in some cases (Arznei-Telegramm, 2013b; McGuire and Wilson, 2013).

Originally developed by the U.S. military and first licensed in Europe over a quarter century ago by F. Hoffmann-La Roche as Lariam® (Croft, 2007a), the innovator product was recently withdrawn from the U.S. market without explanation (Strauch et al., 2011). Generic formulations of mefloquine remain recommended in the U.S. (Centers for Disease Control and Prevention, 2013), but are decreasingly prescribed for the drug's original antimalarial indications (LaRocque et al., 2012; Kersgard and Hickey, 2013). Similarly, while the innovator product remains licensed in many European countries (Arznei-Telegramm, 2013a), certain authorities now recommend its use only as a drug of last resort (Arznei-Telegramm, 2013b; Bisoffi et al., 2013).

Although the adverse neurological effects of mefloquine have been known for nearly a quarter century (World Health Organization, 1989a), the recent emphasis by regulatory authorities of the permanent nature of some of these effects challenges the conventional belief that they are due merely to the long half-life of the drug (Schlagenhauf et al., 2010) and its continued presence in the body. The possibility of permanent neurological sequelae from the use of mefloquine introduces important new considerations for the continued rational use of the drug and calls for an improved effort to better characterize the pathophysiology of these effects.

In this opinion, it is proposed that many of the lasting adverse neurological effects of mefloquine are consistent with the chronic sequelae of a well characterized but idiosyncratic central nervous system (CNS) toxicity syndrome (or toxidrome) common to a number of historical antimalarial and antiparasitic quinolines and associated with a risk of permanent neuronal degeneration within specific CNS regions including the brainstem. Issues in the development and licensing of mefloquine are then considered in the context of historical awareness of the CNS toxicity of related quinoline drugs.

It is anticipated that the information presented in this opinion will aid in the future clinical recognition of the mefloquine toxidrome and its chronic sequelae, and in informing improved regulatory evaluation of mefloquine and related quinoline compounds, particularly as these drugs are investigated for expanded use worldwide for antiparasitic and other indications.

2. Historical evidence of quinoline CNS toxicity

Although not well described in the contemporary literature, the neurological toxidrome observed with mefloquine appears not to be unique to the drug, but instead shares a number of clinical characteristics in common with idiosyncratic CNS toxicity syndromes produced by certain related quinoline derivatives, including drugs that had historically been widely employed as antimalarials and antiparasitics.

While the naturally occurring cinchona alkaloid quinolines were historically well known to cause seemingly reversible neurological effects including symptoms of cinchonism (Taylor and White, 2004), the potential for lasting neurological effects from quinoline drugs was recognized in the mid 1940s, when certain synthetic quinoline antimalarials were found to cause irreversible CNS toxicity. In particular, the synthetic 8-aminoquinolines pamaquine and plasmocid, then both in common use as antimalarials (Manwell, 1949; Benazet, 1963), were linked to an idiosyncratic neurological syndrome accompanied by direct histopathological evidence of CNS neuronal degeneration in human and animal subjects. These drugs induced in the most extreme cases "highly localized degenerative changes in the (CNS) associated with functional derangement" (Smith and Schmidt, 1947). Nearly three decades later the synthetic hydroxyquinoline clioquinol, then in common use as an antiparasitic (Kono, 1971), had also been linked to a related idiosyncratic neurological syndrome again accompanied by histopathological evidence of CNS neuronal degeneration (Shiraki, 1971; Kono, 1975).

In the following sections, the clinical manifestations and histopathological findings associated with idiosyncratic intoxication with these three drugs are reviewed. Although comparable effects have been observed with a large number of other synthetic quinoline derivatives (Schmidt and Schmidt, 1951; Schmidt, 1983), the well-characterized and fairly conserved nature of the extensive CNS neuronal degeneration caused by these three drugs, together with their widespread historical use in antimalarial and antiparasitic therapy, are of greatest relevance in demonstrating the potential for lasting but previously unrecognized neurological effects from mefloquine.

2.1. Pamaquine

Pamaquine, known chemically as 8-(4-diethylamino-1-methylbutylamlno)-6-methoxyquinoline, originally developed by the Germans (British Medical Journal, 1926; The Science News-Letter, 1926) and also known as praequine, plasmochin, or plasmoquine, was initially thought to be free of cinchona-like neurological effects. In use as an antimalarial since the late 1920s (Hardgrove and Applebaum, 1946), a large review of 258 cases of toxic reactions to the drug failed to identify any symptoms suggestive of CNS toxicity (Hardgrove and Applebaum, 1946). However, pamaquine was found in some users to induce similar symptoms of vertigo and photophobia (U.S. Army Medical Department, 1943; Hardgrove and Applebaum, 1946) and visual disturbance (West and Henderson, 1944) to those commonly attributed to the cinchona alkaloids. Benign perceptions of the safety of pamaquine were challenged when a fatal case of human overdose, marked by blurred vision and facial paresthesias, was found at autopsy to have significant neuronal degeneration within specific brain structures including the brainstem. Careful histopathological study revealed extensive focal degeneration of the pontine nuclei, with mild to moderate degeneration of the vestibular nuclei, particularly the medial vestibular nuclei, as well as the nuclei of cranial nerves III, IV, and VI (Loken and Haymaker, 1949).

Although comparable neurological reactions to pamaquine observed in rhesus monkeys had been characterized as reversible (Schmidt and Smith, 1947), on histopathological testing, the drug in small doses was found to produce strikingly similar effects to those observed later in man (Loken and Haymaker, 1949), causing swelling and subtle degeneration in scattered neurons throughout various brainstem nuclei including within the vestibular, supraspinal, ruber, ambiguus, dorsal motor, lateral cuneate, and lateral reticular nuclei, as well as those of cranial nerves III, IV, and VI (Schmidt, 1947). At higher doses, the drug produced more extensive degeneration in these areas (Schmidt, 1947; Schmidt and Schmidt, 1951).

2.2. Plasmocid

The related 8-aminoquinoline plasmocid, known chemically as 8-(3-diethylaminopropylamino)-6-methoxyquinoline, originally developed by the Russians (Findlay, 1950a) and also known as rhodoquine or Fourneau 710 (Findlay, 1950b) was also found in early human use to cause cinchona-like neurological effects including vertigo, paresis and diplopia (Decourt, 1936). A 1945 review of the foreign literature cited a diverse range of more serious neurological effects including severe ataxia, convergence disorder, smoothing of the nasolabial fold, and deviation of the tongue

(Board for the Coordination of Malarial Studies, 1945) suggestive of focal brainstem dysfunction. A review of 76 human cases of neurological effects attributed to plasmocid toxicity found a range of lasting deficits, including in equilibrium, coordination, and eye muscle movement; some of these symptoms "persisted for months or years after termination of treatment" (Schmidt and Schmidt, 1949).

In the absence of published neurohistopathological testing of fatal human cases of plasmocid intoxication, early neurological effects were commonly attributed to cerebellar ataxia, polyneuritis, and optic atrophy (Findlay, 1950b). However, histopathological testing in rhesus monkeys following administration of high doses of plasmocid revealed almost complete destruction of the nuclei of cranial nerves III, IV, and VI and of the vestibular nuclei; further administration produced variable patterns of injury extending into other brainstem nuclei (Schmidt and Schmidt, 1947; Lyle and Schmidt, 1962), with highly scattered lesions extending throughout the medulla, pons, striatum, and limbic system (Schmidt and Schmidt, 1948; Sipe et al., 1973). Authors speculated that "the effect of plasmocid on the human brain would be quite similar" to that observed in monkey (Sipe et al., 1973), and that multiple human cases of CNS toxicity were "doubtless similar to these in origin" (Schmidt, 1983).

2.3. Clioquinol

By the early 1970s, accumulating evidence with the antiparasitic hydroxyquinoline clioquinol, known chemically as 5-chloro-7-iodo-8-quinolinol, had demonstrated a similar propensity for CNS toxicity to that observed with antimalarial 8-aminoquinolines. Although idiosyncratic cases of human toxicity, labeled subacute myelo-optic neuropathy (SMON) (Kono, 1971) are characteristically associated with symptoms attributable to peripheral neurotoxicity, cases of SMON have also featured disequilibrium (Ferrier and Eadie, 1973), visual disturbances (Kaeser, 1984), paresthesias and gait disturbances (Tsubaki et al., 1971), and vertigo and nystagmus (Yamasaki and Shibuya, 1968) equally attributable to CNS causes.

Although the neurohistopathology of SMON has been more typically characterized by extensive degeneration within the dorsal columns and the optic nerve, extensive evaluation of autopsy cases has also revealed degeneration of brainstem structures including the inferior olive and nucleus ruber (Kono, 1975); the roots of cranial nerves V, VIII, and X (Shiraki, 1971); and the nucleus gracilis (Ricoy et al., 1982). On histopathological study across animal models, the drug produces scattered and highly variable degenerative lesions including within the distal optic nerve and dorsal funiculus of the spinal cord (Hoover et al., 1981) and fasciculus gracilis (Tateishi et al., 1972a) in beagle dogs; the optic tract and fasciculus gracilis in cats (Tateishi et al., 1972b); and the nucleus gracilis in rats (Arasaki and Nakanishi, 1989).

3. Evidence of mefloquine CNS toxicity

The most prominent neuropsychiatric effects identified during the development of mefloquine including vertigo initially resembled those of cinchonism induced by quinine (Stockwell, 1982; World Health Organization, 1989b). Presumably due to lack of direct histopathological evidence of quinine neurotoxicity and the presumed transient nature of neurological effects from drugs of the 4-quinolinemethanol class (Schmidt et al., 1978a,b), the drug appears to have been assumed free of the known permanent CNS toxicity of pamaquine, plasmocid, and clioquinol.

The neurotoxicity of mefloquine was only first reported in papers published more than three decades after the drug's reported synthesis (Ohnmacht et al., 1971), following experiments in cultured rat neuroblastoma and embryonic rat neuron cell lines (Dow, 2003) over a range of neurophysiologically plausible concentrations (Dow et al., 2003). In subsequent years, confirmatory evidence of the drug's neurotoxicity was also obtained (Dow et al., 2004, 2005; Caridha et al., 2008).

In direct histopathological testing in a rat model, high dose mefloquine induced neuronal degeneration evocative of the effects of clioquinol in the nucleus gracilis, nucleus cuneatus, and solitary tract (Dow et al., 2006), and was accompanied by "anxiousness/hyperactivity" and functional changes in motor activity (Dow et al., 2006). Study authors noted that the brainstem injury induced by mefloquine was "permanent in nature" (Dow et al., 2006). Independent authors subsequently demonstrated mefloquine neurotoxicity in rat cortical neurons (Hood et al., 2010; Milatovic et al., 2011) and in human neuronal cell lines (Geng et al., 2010; Shin et al., 2012). While recommended confirmatory human neurohistopathological testing has yet to be performed (Nevin, 2009), clinical observations following intoxication from mefloquine at prophylactic doses have demonstrated lasting deficits consistent with brainstem lesions or dysfunction in the vicinity of the oculomotor and vestibular nuclei (Nevin, 2012a).

While a variety of pathological mechanisms may be evoked to explain many of the signs and symptoms associated with mefloquine use, CNS neuronal degeneration similar to that observed in the animal model and similar to that caused by pamaquine and clioquinol in humans provides a highly parsimonious theoretical explanation for many of the drug's reported chronic neurological effects, including lasting cases of vertigo (Grupp et al., 1994), disequilibrium (Nevin, 2012a), and paresthesias (Lobel et al., 1998).

For example, although mefloquine is a known peripheral ototoxicant (Yu et al., 2011; Ding et al., 2013), focal neuronal degeneration in the vicinity of the oculomotor and vestibular nuclei (Nevin, 2012a), as observed at human autopsy with pamaquine and in animal models from plasmocid, provides a parsimonious pathophysiological explanation for at least some of the reported chronic vestibular effects of mefloquine. Similarly, while symptoms of mefloquine neuropathy have frequently been attributed to peripheral causes (Watt-Smith et al., 2001; Jha et al., 2006) including to C-fiber irritation (Chester and Sandroni, 2011), the lack of direct evidence of specific peripheral neurotoxicity, together with the drug's demonstrated degenerative effects in the animal model in areas of the brainstem involved in the processing of sensory inputs including the nucleus gracilis, cuneatus and solitary tract (Dow et al., 2006) suggest that CNS toxicity, analogous to that observed historically with clioquinol, may provide a more plausible and parsimonious pathophysiological explanation for these symptoms.

In spite of the large and growing body of neurotoxicity data from *in vivo* and *in vitro* studies, broader acceptance of the possibility of clinically significant CNS neurotoxicity from mefloquine has remained strangely elusive in the literature, possibly owing to the absence of published human neurohistopathology studies (Nevin, 2009). Interestingly, in the absence of comparable human neurohistopathology, and on the basis of animal studies alone, clinically significant human CNS neurotoxicity from plasmocid was never seriously contested and was even deemed "doubtless" by leading historical authorities (Sipe et al., 1973; Schmidt, 1983). In contrast, some contemporary authors have appeared less inclined to acknowledge the possibility of similar effects from mefloquine, particularly at the relatively low doses encountered during prophylactic use, claiming that extrapolation of high dose neurotoxicity data from animal studies to human cases still requires the "bridging of a large knowledge gap" (Schlagenhauf et al., 2010).

Fortunately, human neuropharmacokinetic data is available that may effectively bridge this gap. For example, human autopsies have demonstrated mefloquine CNS accumulation at prophylactic dosing

rates (Jones et al., 1994; Clifford et al., 2013) to concentrations comparable to those after treatment (Pham et al., 1999) and well beyond *in vitro* human cell line neurotoxicity thresholds (Geng et al., 2010; Shin et al., 2012). Additional *in vivo* (Barraud de Lagerie et al., 2004) and pharmacogenetic studies (Aarnoudse et al., 2006) provide further neuropharmacokinetic insights into known CNS drug transport (Pham et al., 2000) and metabolism (Fontaine et al., 2000) pathways that may plausibly mediate idiosyncratic accumulation in CNS to neurotoxic concentrations during routine use.

Despite both toxicological and pharmacokinetic plausibility, demonstrating incontestable evidence of mefloquine CNS toxicity in individual clinical cases remains challenging. With use of mefloquine at higher doses for treatment of malaria, the possible confounding of signs and symptoms of CNS toxicity by those of comorbid cerebral malaria (Weiss, 1985) creates challenges for their attribution uniquely to the drug. Similarly, with use of mefloquine at lower prophylactic doses, a lack of sensitive prospective ascertainment, particularly in resource-constrained settings, may result in neurological effects not being identified (Rønn et al., 1998). Even when such effects are identified, demonstrating incontestable evidence of CNS toxicity may be made challenging by the microscopic and highly focal nature of most expected neuronal degeneration (Dow et al., 2006), which as with presumed cases of clioquinol CNS toxicity (Kimura et al., 2011), would be frequently undetectable by conventional neuroimaging. Despite these limitations, reports of highly specific clinical findings, including central vestibulopathy (Nevin, 2012a) occurring among those without any history of malaria or other plausible neurological etiologies establishes mefloquine CNS toxicity as a probable pathophysiological entity worthy of significant further investigation, particularly as the drug is considered for expanded use against parasitic disease and for other indications.

4. Mefloquine CNS toxicity in historical context

The long delayed recognition of the possibility of clinically significant CNS toxicity from mefloquine calls for an examination of the historical context of the drug's development and licensing as an antimalarial. Although the first synthesis of mefloquine, known chemically as 2,8-bis(trifluoromethyl)-(2-piperidyl)-4-quinolinemethanol, was reported in 1969 (Ohnmacht et al., 1971), the drug was very closely related to the synthetic 4-quinolinemethanol compound 4-quinolyl-α-piperidylcarbinol first reported over three decades earlier in 1938 (Ainley and King, 1938). Mefloquine differs from this previously synthesized compound (later known as SN 2549) (Berliner et al., 1946, p. 1062) solely by addition of two trifluromethyl groups (CF_3) at the 2 and 8 positions of the quinoline nucleus.

During early human testing of the 4-quinolinemethanols during the U.S. military's World War II era drug discovery program (Alving et al., 1948) these drugs exhibited some evidence of the CNS toxicity observed from related synthetic quinoline compounds (Schmidt and Schmidt, 1951), including producing visual photosensitivity or photophobia (Pullman et al., 1948). One particularly efficacious 4-quinolinemethanol known as SN 10,275 induced headache and visual photosensitivity (Pullman et al., 1948) but also induced phototoxicity which may have masked recognition of underlying CNS effects. Presumably owing to concerns of phototoxicity (Rozman and Canfield, 1979; World Health Organization, 1984), investigation of 4-quinolinemethanols as antimalarials was formally abandoned in favor of the more promising 4-aminoquinolines (Schmidt et al., 1978a).

However, by the early 1960s (Tigertt, 1969), owing ostensibly to concerns of rising resistance to the 4-aminoquinoline chloroquine, the U.S. military had initiated a new large scale drug discovery program (Modell, 1968), during which time hundreds of thousands of compounds were evaluated for their antimalarial activity. Over 300 4-quinolinemethanols were evaluated in this effort, including some that had been previously tested during the earlier wartime program (Schmidt et al., 1978a). Mefloquine (initially known as WR 142,490) quickly emerged as the favored of these drugs based the results of limited human testing in prisoners (Rieckmann et al., 1974; Trenholme et al., 1975) that suggested the drug was free of serious side effects. Soon after its first reported synthesis, mefloquine had been singled out by the U.S. military for larger-scale synthesis (Ohnmacht et al., 1971) and commercialization by F. Hoffmann-La Roche (Maugh, 1977). So rapid was the testing of the drug in field settings that one researcher noted "Phase II clinical trials threatened to outstrip needed Phase I testing" (Reba, 1977).

When the experimental 4-quinolinemethanol compounds WR-184,806 and WR-226,253 were noted in the early 1970s to evoke lightheadedness and difficulties in focusing (Schmidt et al., 1978b), these symptoms appear not to have been taken as evidence of possible CNS toxicity of the 4-quinolinemethanol class. Similarly, during testing of mefloquine, early and frequent reports of vertigo (Harinasuta et al., 1983; Björkman, 1989), "dizziness" (Trenholme et al., 1975; Harinasuta et al., 1983; Reisinger et al., 1985), and rare but sentinel reports of formication (Harinasuta et al., 1983), psychosis (Harinasuta et al., 1983; Björkman, 1989), confusion (Harinasuta et al., 1985; Nosten et al., 1987; Bernard et al., 1989; Björkman, 1989), amnesia (Lapras et al., 1989), and gait disturbance (Harinasuta et al., 1983) were seemingly also not considered in the context of earlier publications as evidence of potentially permanent CNS toxicity (Schmidt et al., 1978a). Importantly, and in marked contrast to the extensive testing conducted during earlier wartime drug development efforts (Schmidt and Coatney, 1955), no significant histopathological testing appears to have been undertaken prior to the U.S. licensure of mefloquine to rule out the drug's potential neurotoxicity.

Despite the lack of specific neurohistopathological testing, there nonetheless appears to have been clear awareness of the drug's potentially serious CNS effects. The original 1989 U.S. product insert acknowledged a risk of "disturbed sense of balance", and "visual disturbances", and cautioned that during prophylactic use, "if signs of unexplained anxiety, depression, restlessness or confusion are noticed, these may be considered prodromal to *a more serious event*" (emphasis added). Although this critical phrase was left undefined, the product insert warned of a risk of CNS disturbances including "encephalopathy of unknown etiology" during prophylactic administration (Hoffmann-La Roche, 1989). In subsequent years, absent empiric understanding of the molecular basis of mefloquine's CNS effects, multiple authors posited imaginative but ultimately untested theories to explain the drug's marked neuropsychiatric toxicity (Croft and Herxheimer, 2002; Nevin, 2009; Mawson, 2013).

Although evidence suggestive of the neurotoxicity of mefloquine was published in 1996 (Lee and Go, 1996), it was only in 2003, 14 years after the drug's U.S. licensure, that the first results of neurotoxicity testing in rats were published by U.S. military affiliated researchers (Dow et al., 2003). Recent attempts to mitigate mefloquine neurotoxicity, including efforts sponsored by the U.S. military to develop a human "safety test" (Walter Reed Army Institute of Research, 2006) to identify individuals with idiosyncratic susceptibility, have thus far failed to yield satisfactory results. Notwithstanding recent confusion over the absolute configuration of the currently marketed drug (Ding and Hall, 2013; Schützenmeister et al., 2013), randomized trials of enantiomeric mefloquine (Knight et al., 2011), originally thought less likely to

induce CNS effects owing to slightly lower average brain accumulation (Baudry et al., 1997; Dow et al., 2011), have also demonstrated a propensity similar to the currently licensed racemic mixture to induce idiosyncratic "centrally mediated" symptoms of "dizziness" and difficulties in concentration (Tansley et al., 2010).

With rising awareness of the drug's neurotoxicity, by 2009, the U.S. military had prohibited the widespread use of mefloquine for prophylaxis (Milatovic and Aschner, 2011), and had returned to a policy of first-line use of doxycycline (Nevin, 2012b), the drug of choice prior to the U.S. licensing of mefloquine 20 years earlier (Sánchez et al., 1993). In response to the FDA boxed warning, senior U.S. military officials recently emphasized that mefloquine should be used for prophylaxis only as a "drug of last resort" (Woodson, 2013), while elite U.S. military units prohibited such use of the drug outright (Reactions Weekly, 2013).

While never explicitly addressing the potential implications of permanent CNS toxicity from the drug, senior U.S. military medical authors have acknowledged that mefloquine's neuropsychiatric effects might "confound the diagnosis and management of post-traumatic stress disorder and traumatic brain injury" making "the continued routine use of mefloquine less desirable" (Magill et al., 2012), and noting that "with the availability of better-tolerated drugs, there is no need to use mefloquine for treatment unless other options are unavailable" (Magill, 2006).

The near complete withdrawal of mefloquine within the U.S. military both for prophylaxis and treatment clearly marks the demise of the drug for the military indications for which it was original developed (Croft, 2007a). Interestingly, in 1978, a leading authority involved in the development of mefloquine had noted that the drug "promises to be broadly useful" in the treatment and prophylaxis of malaria, but that "[if] this promise is not realized, it will doubtless not be for lack of antimalarial activity, but rather because of toxicological attributes not identified in the small-scale studies pursued to date" (Schmidt et al., 1978a). Two decades earlier, during testing of related 8-aminoquinoline antimalarials (Schmidt and Coatney, 1955), this same authority had presciently cautioned that since "...in doses well below the lethal level [these drugs] produced striking symptoms of [CNS] injury associated with severe lesions in the principal nuclei of the proprioceptive, visual-reflex, and vestibulo cerebellar pathways... their capacity to evoke reactions which might mask symptoms of low grade neuronal injury, plus the likelihood of their widespread use in malaria therapy, make a detailed search for CNS lesions highly desirable" (Schmidt and Schmidt, 1951). With awareness of the potential for lasting CNS toxicity finally emerging over 40 years after mefloquine's initial development, it appears worthy of further investigation to determine precisely why such a "highly desirable" search was never performed, and why pre-licensure testing appears to have been limited only to "small-scale" studies.

5. Conclusions

In this opinion, it has been argued that many of the idiosyncratic chronic neurological sequelae associated with mefloquine use not only have a solid biological basis, but are consistent with a more generalized CNS toxicity syndrome common to certain historical quinoline drugs and associated in both animal and human studies with a risk of neuronal degeneration particularly within specific brainstem nuclei. In the four decades since the development of mefloquine, and absent seeming awareness of its potential to induce permanent CNS toxicity, many of the drug's most severe idiosyncratic neuropsychiatric effects have been attributed by influential authors to the stresses of travel or to latent or pre-existing mental illness (Lobel, 1996; Schlagenhauf et al., 1997; Schlagenhauf, 1999; Schlagenhauf and Steffen, 2000), or to "media hype" (Schlagenhauf, 1996). With the benefit of the insights presented in this opinion, these prior explanations for many of mefloquine's reported adverse effects now appear unsatisfactory.

The recent emphasis by regulatory authorities of the potential for permanent neurological effects from mefloquine, coming four decades too late to rationally inform most antimalarial use of the drug, underscores the need for sensitive prospective evaluation (Rønn et al., 1998) of neurological endpoints during clinical testing as the drug is repositioned for possible widespread antiparasitic use, including in the treatment of schistosomasis. However, given the clinically occult CNS toxicity that may result from use of mefloquine, the insights of this opinion also underscore the critical importance of better characterizing the molecular basis of quinoline neurotoxicity, and emphasize the need to ensure comparable neurohistopathological testing (Schmidt and Schmidt, 1951) is performed in appropriate animal models prior to the future licensing of related quinoline drugs.

Such testing appears particularly needed for tafenoquine (Nasveld et al., 2010), an 8-aminoquinoline initially developed by the U.S. military (Kitchen et al., 2006) and related structurally both to pamaquine and plasmocid, and associated in pre-licensing trials with a similar risk of vertigo as mefloquine (Nasveld et al., 2010). While tafenoquine has been eagerly anticipated for its utility against vivax malaria (Baird, 2012) and potentially against leishmaniasis (Manzano et al., 2011a,b), the recent granting by the U.S. FDA of Breakthrough Therapy (Sherman et al., 2013) status, in the absence of any published neurohistopathological testing, risks recreating the sense of urgency that contributed to the approval of mefloquine in the absence of appropriate CNS safety data (Croft, 2007a,b).

Lastly, although of incidental interest to the parasitology community, these insights also suggest the need for caution as mefloquine (Nevin, 2011) and other currently licensed antiparasitic and antimalarial quinoline drugs are increasingly evaluated for treatment of neuropsychiatric and neurologic conditions, including behavioral dyscontrol (Daly and Caplan, 2012), affective dysregulation (Stahl, 2013), chorea (Ondo, 2012), progressive multifocal leukoencephalopathy (Clifford et al., 2013), multiple sclerosis (Nevin, 2012c), and glioblastoma (Geng et al., 2010), which might plausibly mask or make difficult the recognition of CNS toxicity and low grade neuronal injury.

Disclaimer

The author has been retained as a consultant and expert witness in legal cases involving claims of antimalarial drug toxicity.

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A lesson learnt: the rise and fall of Lariam and Halfan

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J R Soc Med 2007;**100**:170–174

INTRODUCTION

Lariam (pharmacological name mefloquine) is an antimalaria drug discovered by the US Army shortly after the Vietnam War, and subsequently marketed worldwide by F. Hoffmann-La Roche. The first reported trials of mefloquine were in prisoners, and were performed at the Joliet Correctional Center, Illinois, in 1975, and at the Maryland House of Correction in 1976.[1,2]

Halfan (pharmacological name halofantrine) is an antimalaria drug chemically related to mefloquine and quinine. Like Lariam, Halfan emerged from the US Army's huge post-Vietnam antimalaria drug discovery programme.[3] Halfan was first described in the literature in November 1982.[4] During the 1980s and 1990s, Halfan was marketed by Smith Kline Beecham.

There is no question that safe and effective antimalaria drugs were needed in the second half of the twentieth century, once it became apparent that the *Plasmodium* had developed resistance to the mainstay of antimalaria therapy, namely chloroquine. Chloroquine resistance was observed first in Thailand in 1957, then on the Colombian-Venezuelan border in 1959, and in Kenya and Tanzania in 1978.[5] Within a decade of Lariam and Halfan being marketed, however, the safety of both these novel agents was in doubt.

This essay looks at the unusual developmental history of Lariam and Halfan, explains the circumstances under which both drugs rose in esteem with policy makers and prescribers and then fell into disfavour with consumers, and summarizes the lessons learnt in the process. These lessons need to be recorded and acted upon, to prevent a repetition of the same mistakes with the next generation of antimalaria compounds.

BACKGROUND

Both Lariam and Halfan were discovered at the Experimental Therapeutics Division of the Walter Reed Army Institute of Research (WRAIR) in Washington DC.[3] In the earliest published reports, these two drugs had not yet been named, and they were still referred to by their respective Walter Reed experimental numbers: WR 142 490 and WR 171 669.[1,4] Lariam and Halfan were the two main progeny of the WRAIR malaria drug discovery programme, which ran from 1963 until 1976.

Over a 15-year period, vast resources were voted by the US federal government to fund WRAIR's antimalaria drug research, which at the time was the largest drug discovery programme ever mounted. The political driving force behind the programme was the severe clinical setback experienced by the US military during the Vietnam War, when at one stage 1% of US combat troops were succumbing to malaria each day.[6] Because of the size and urgency of the research task, WRAIR collaborated with numerous governmental, academic and commercial organizations, including 175 external contractors.[7]

From the early 1960s onwards, WRAIR screened over 250 000 potential antimalaria compounds.[8] Lariam was number 142 490 in this long series, and Halfan was number 171 669. Because the US military was and remains forbidden by Congress from operating in the commercial sector, WRAIR engaged the holding companies F. Hoffmann-La Roche and Smith Kline Beecham to market these two promising novel agents.

The precise details of the three-way business agreement between WRAIR, the US federal government and the two multinational drug companies which marketed Lariam and Halfan have not been made public. It appears, however, that all of WRAIR's phase I and phase II clinical trial data on Lariam and Halfan were delivered as a free good to F. Hoffmann-La Roche and to Smith Kline Beecham. Drug approval was swiftly granted by the Food and Drug Administration (FDA): Lariam was approved in 1989 and Halfan in 1992.

From the perspective of the two drug companies chosen to act as the marketing arm of WRAIR, the primary commercial potential of Lariam and Halfan lay in their ability to prevent malaria in tourists and business travellers to the tropics. Prior to their obtaining FDA approval, however, no randomized Phase III tolerability study was carried out on either drug in a normal study population of healthy civilian volunteers.[9] Likewise, there was no serious attempt prior to licensing to explore the potential drug-drug interactions of either Lariam and Halfan; some of the fatal drug reactions which followed may have been a direct

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consequence of the resulting gap in the prescribers' knowledge base.

Within months of their being licensed, major safety concerns around Lariam and Halfan began to emerge. These two compounds should have been welcomed by the public as being safe, effective and lifesaving pharmaceutical weapons in a world where international travel was increasing exponentially and where chloroquine-resistant malaria seemed to be spreading just as rapidly.[10] Instead, consumers viewed the two new drugs with disquiet, and later with concern and alarm.

THE SITUATION TODAY

Though still prescribed in most countries, both for preventing and treating malaria, Lariam is now known to cause neurotoxicity.[11] This unexpected property came to prominence in the mid-1990s, when national pharmacovigilance centres, initially in Europe, began to receive recurring reports of neuropsychiatric adverse effects caused by this new antimalaria agent. In the Netherlands during 1998 and 1999, mefloquine was respectively the most and the second most cited drug in spontaneous reports of drug-related illness made to the Lareb Pharmacovigilance Foundation.[12] Around the same time, it was reported that 60% of all the mefloquine occurrences notified to the WHO's Uppsala Monitoring Centre cited neuropsychiatric disturbance secondary to the drug.[12]

Belatedly, three randomized controlled trials were carried out in healthy volunteer populations, and were reported between 2001–2003.[13-15] The studies confirmed mefloquine's potential for causing psychological illness, and all three study reports described an excess of neuropsychiatric adverse effects in the mefloquine arm.[13–15] Around the same time an analysis of the cause of illness in 4524 travellers returning from sub-Saharan Africa to the northern hemisphere found that, excluding diarrhoea and fever as causes, mefloquine was the fifteenth most common cause of post-travel illness.[16] A case control study of 564 Dutch travellers between 1997 to 2000 found a threefold increase in the incidence of psychiatric events with mefloquine use (OR 3.5, 95% CI 1.4–8.7), and a very high risk of psychiatric events in women users of the drug (OR 47.1, 95% CI 3.8–578.6).[17] A survey of the recent literature shows that mefloquine has been causally associated with 19 deaths in users, including three suicides (Table 1).[18–26]

By 2004, public concern in the US was such that the FDA took the exceptional step of insisting that a patient medication guide be given to all recipients of mefloquine prescriptions.[27,28] The FDA thus followed the example of the Committee on Safety of Medicines, which had advised British doctors in 1996 to warn patients about the incidence of neuropsychiatric adverse effects with mefloquine. As was pointed out in the *British Medical Journal*, this advice overturned accepted clinical practice in the UK, which at that time was to warn patients about common adverse effects only.[29,30]

Table 1 **Nineteen deaths causally associated with Lariam (mefloquine) use**

Reference	*Patient nationality*	*Patient age*	*Clinical details*
18	American (USA)	Not stated	After one mefloquine tablet, patient experienced cardiopulmonary arrest, death.
19	Thai	13	Malaria recrudesced 21 days after mefloquine treatment. Given halofantrine over 3 days. Experienced sudden cardiac arrest, death.
20	British	6	Developed blistering of lips and oral mucosae. Generalized erythema and blistering, then exfoliation of the mucosae. Ulceration of the mucosae, hair and nail loss. Cardiac asystole, death.
21	British	37	After taking Lariam for overseas trip, became acutely depressed. Committed suicide by jumping to his death from the roof of a mansion block.
22	German	33	Took two Lariam tablets for suspected malaria. After 4 hours, experienced headaches, 'burning in bones', deafness, dizziness. Confused, panic, depression. Hospitalized. Committed suicide.
23	American (USA)	22	Early during mefloquine prophylaxis, experienced fever (102 degrees), chills, headache, cough. Initially treated as malaria. Then, during a 2-hour car ride, experienced a 'head rush.' Collapsed, died.
24	British	Not stated	Eight fatal reactions to mefloquine, reported to the UK Medicines Control Agency.
25	Not stated	Not stated	Four fatal reactions to Lariam, recorded on the manufacturer's database of adverse drug reactions.
26	French	27	Treated with Lariam for 48 hours. Committed suicide 6 weeks later, through self-inflicted multiple knife wounds.

Also unexpectedly, Halfan was found after licensing to cause ventricular dysrhythmias that were often fatal.[23,31–33] This unforeseen property of the drug (unforeseen because unresearched) came to light serendipitously, in a prospective electrocardiographic study of Karen patients that was reported in the *Lancet* in 1993.[34] Halfan is no longer recommended by WHO for the self-treatment of malaria, and the drug is not listed for this indication in the *British National Formulary* or in other national pharmacopoeias. Halfan is not now approved in any country for malaria prophylaxis.[35] The 2006 edition of *Goodman and Gilman* states that:

> *'Because halofantrine displays erratic bioavailability, potentially lethal cardiotoxicity, and extensive cross-resistance with mefloquine, its use generally is not [now] recommended.'*[36]

The disappointing performance in clinical practice of these two drugs, developed at enormous cost to the US taxpayer, could not have been anticipated 30 years ago. Or could it?

WHAT WENT WRONG?

Both Lariam and Halfan are products of what has been called 'the military-industrial complex'. This is an overused term, but one that describes a real entity.

The partnership between industry and the military has achieved some astonishing technical feats—witness the placing of a man on the moon. In the area of patient care, however, the health and wellbeing of consumers of health care is protected by regulations which, however imperfect and seemingly cumbersome, are derived from decades of use and experience. These regulations reach forward in time, protecting future cohorts of patients from prescriber-induced harm, but also slowing up pharmaceutical innovations which in some cases may be needed urgently. Powerful lobbies, impatient of delay (and acting in what they may see as the public's best interests) may be tempted to disregard those regulations. The clinical consequences of doing so may be unforeseen, however.

As stated above, the underpinning safety and pharmacokinetic studies which should have been performed prior to the licensing of Lariam and Halfan, on the main intended target group for both drugs (namely, tourists and business travellers), were never carried out.[9]

In the case of Lariam, the first randomized controlled trial of the drug in a mixed population of general travellers was not reported until 2001.[13] Of the study participants randomized to receive mefloquine, 67.1% reported $\geqslant 1$ adverse event, and in 6% of mefloquine users these events were severe (defined as requiring medical advice). Had this same understanding of mefloquine been available prior to its licensing, as it should have been, it is certain that the FDA and the other national licensing authorities which approved Lariam for use prophylactically, in and around 1989, would not at the time have endorsed this drug.[37]

It seems probable that in the late 1980s and early 1990s the FDA and other national licensing bodies were influenced, perhaps subliminally, by the powerful military-industrial-governmental lobby into over-hasty decisions to approve the marketing of both Lariam and Halfan. These two drugs were authorized for public use on the basis of an incomplete knowledge base, and at too early a stage in the normal cycle of drug development.

Post-marketing surveillance of Lariam and Halfan took the place of normal, responsible, pre-licensing research into the safety of these two agents.

Travel medicine experts in most countries were slow to recognize the danger signals associated with Lariam and Halfan, and for many years the public's concern about Lariam, in particular, was dismissed as 'media hype'. A senior WRAIR scientist, writing in 2001, deplored what he called ' . . . the ''herd mentality'' of mefloquine associated psychoses', and stated defiantly that 'mefloquine (Lariam®) remains the prophylaxis of choice for US soldiers and travellers.'[38] As late as 2005 a reviewer in the *New England Journal of Medicine*, also an employee of the US military for over 20 years, continued to maintain, in the face of compelling empirical and experimental evidence to the contrary, that Lariam was a 'well tolerated' drug.[39] However, by the following year a US military research team, based partly at WRAIR, conceded that:

'Walter Reed Army Institute of Research is currently investigating mefloquine analogues, seeking one with similar efficacy but reduced neuropsychiatric toxicity.'[3]

The victims of this pharmacological muddle have been those many business travellers, embassy staff, tourists, aid workers, missionaries, soldiers and others who were well at the start of their journeys into malaria-endemic areas, were prescribed Lariam or Halfan by their physicians, and who then suffered unforeseen (because unresearched) harms from their chemoprophylaxis.

Effectively, all users of Lariam and Halfan, from the point of licensing onwards, have been involved in a natural experiment to determine the true safety margin, at current dosages, of these two poorly understood antimalaria drugs. Consumers have been unwitting recruits to this longitudinal study, rather than informed partners.[9,40] The rapid public rejection of Lariam and Halfan could have been anticipated, since users of malaria chemoprophylaxis differ from normal patients in that they are by definition healthy people, and on this account they are unwilling to accept even relatively minor drug-related harms.[41]

Ironically, for a drug that was discovered by the military, soldiers have been amongst the most vocal critics

of Lariam. Following a Parliamentary enquiry, Canada's auditor general condemned protocol abuses in which 900 Canadian soldiers deploying to Somalia were prescribed Lariam in 1992–1993, at a time when the drug was still unlicensed in Canada.[42] In the Netherlands, reports of severe adverse drug reactions in soldiers who had used Lariam prophylaxis while undertaking peacekeeping duties in Cambodia prompted questions in Parliament and intense public debate.[43] In the US, military epidemiologists have investigated the possible role of Lariam in a series of murders and suicides among soldiers in North Carolina who had served in Afghanistan.[44] Most recently, the Australian military has been threatened with legal action by soldiers reporting severe and disabling symptoms which they attributed to Lariam prophylaxis.[45]

THE FUTURE

Sir Iain Chalmers has pointed out how the biased under-reporting of research harms and sometimes kills patients.[46] The under-reporting of research, he states, is essentially a form of misconduct, since it can lead to seriously misleading recommendations for clinical practice and for new research.[47]

The case of Lariam and Halfan does not exactly fit the model of scientific irresponsibility which has been highlighted by Chalmers and others. It is not the case, with these two antimalaria agents, that inconvenient research data on their adverse effects was deliberately withheld from national drug licensing authorities, and from the public. The necessary pre-licensing research was simply never carried out.

The prime lesson from the Lariam and Halfan experience is that drugs intended primarily for use by healthy people must be genuinely well tolerated, and indeed they must demonstrate much better tolerability under their actual conditions of use than would normally be required for, say, antimitotic agents. Future research studies of malaria chemoprophylaxis must address the unanswered questions and outstanding gaps in the evidence.[48] In particular, planned research studies must be carried out on the population of interest (that is, on tourists and business travellers) and not on a convenience sample of prisoners, or soldiers.[49]

Despite the public outcry about Lariam and Halfan, it is extraordinary that no real attempt has yet been made to properly explore the adverse effects of these two drugs in terms of what causes these effects, who is likely to experience them, how long the effects typically last, how the effects can be mitigated, and how they should be managed if they do occur.

There are several plausible mechanisms through which the unwanted effects of Lariam and Halfan, which are structurally related quinoline derivatives, might be mediated. Croft and Herxheimer suggested in 2002 that many of the adverse effects of mefloquine may be a post-hepatic syndrome caused by primary liver damage, with a subset of mefloquine users also experiencing thyroid disturbance.[50] More recently, Aarnoudse and colleagues have hypothesized that the neuropsychiatric effects of mefloquine are associated with polymorphisms in the MDR1/ABCB1 gene that encodes for the efflux pump P-glycoprotein.[51] Both theories remain speculative, however, since the rigorous studies needed to test the respective hypotheses have not yet been carried out.

Because the harms of mefloquine have never been adequately investigated, and because there appears to be no incentive for the manufacturer of Lariam ever to do this, it is likely that mefloquine, which like halofantrine is a potentially important weapon in the limited pharmaceutical arsenal against malaria, will be discarded along with its sister drug. A recent British review of the treatment options for malaria does not mention mefloquine at all.[52] This apparent willingness to casually sideline two undoubtedly lifesaving drugs represents a waste of resources, and a loss also to future travellers and patients. Researchers, policy makers and prescribers must learn from this experience or be condemned to repeat it. Many of the individual medical tragedies detailed in the table need never have occurred. Powerful institutional pressures must never again override the needs and rights of patients.[46,47]

Competing interests None declared.

Acknowledgments This essay was the Prize Winner in the RSM Section of Pharmaceutical Medicine & Research Prize Essay Competition 2006. I am grateful to the sponsors of the Prize and to all those fellow scientists who helped me develop the ideas outlined in this essay. The opinions expressed here are my own.

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MEFLOQUINE NEUROTOXICITY, COMMONWEALTH DUTY OF CARE AND VETERANS' MENTAL HEALTH: A CASE FOR PROACTIVE OUTREACH

Major Stuart McCarthy January 2015

Abstract

Mefloquine is an anti-malarial drug which, despite its neurotoxicity and neuropsychiatric side effects, has been widely used by Australian Defence Force (ADF) personnel for many years. Although the manufacturers, the ADF and other authorities have long acknowledged these side effects, the conventional wisdom has been that they are only temporary. However there is now strong evidence not only that the drug's side effects can be long term or even permanent, but that they may indeed have contributed to widespread misdiagnosis, and subsequent mistreatment, of many ADF veterans with health problems such as post traumatic stress disorder (PTSD) and traumatic brain injury (TBI). Such misdiagnosis and mistreatment poses an ongoing threat to the health and wellbeing of many veterans. The ADF, Department of Veterans Affairs (DVA) and other Commonwealth Government agencies now have a duty of care to address this problem by implementing a program of proactive outreach to affected veterans, which could number in the thousands.

> *"The US Food and Drug Administration (FDA) is advising the public about strengthened and updated warnings regarding neurologic and psychiatric side effects associated with the antimalarial drug mefloquine hydrochloride. A boxed warning, the most serious kind of warning about these potential problems, has been added to the drug label. … Neurologic side effects can occur at any time during drug use, and can last for months to years after the drug is stopped or can be permanent."*
>
> US FDA, *Drug Safety Communication*, 29 August 2013[1]

> *"We now recognize, decades too late, that mefloquine is neurotoxic and can cause lasting injury to the brainstem and emotional centers in the limbic system. As a result of its toxic effects, the drug is quickly becoming the 'Agent Orange' of this generation, linked to a growing list of lasting neurological and psychiatric problems including suicide."*
>
> Dr Remington L. Nevin, 25 September 2013[2]

> *"The UK MoD should follow the US example and no longer prescribe Lariam. The risks are too high. There are enough other pressures on service people that could cause mental-health issues. We do not need a prescribed drug adding to the risk."*
>
> General Lord Richard Dannatt, former UK Chief of the General Staff
> 27 September 2013[3]

Introduction

Mefloquine hydrochloride (trade name *Lariam*) is a quinoline-derived drug that has been widely used for malaria prophylaxis by military forces, including the ADF.[4] The neurotoxic properties of the drug and its neuropsychiatric side effects have long been acknowledged by manufacturers and health authorities including the Surgeon General ADF (SGADF), however conventional wisdom has been that these side effects are only temporary.[5] Recent scientific-medical research now indicates that the side effects can in fact be long term or permanent,[6] and there is a growing body of evidence that many veterans are adversely affected. Not only should the ADF re-consider its use as an anti-malarial drug but, more importantly, both the ADF and DVA need to assess its impact on the health of personnel who were administered this drug during their service; particularly for those who served in Iraq, Afghanistan and/or other recent conflicts and who then experienced long term mental health problems which may have been misattributed to their operational experiences rather than mefloquine neurotoxicity.

This paper outlines the historical development of mefloquine and its use by military forces including the ADF, summarises the contemporary research on its neurotoxicity and neuropsychiatric side effects, explains how these side effects may be compounding the wave of mental health problems experienced by veterans of Iraq, Afghanistan and other recent conflicts, then proposes a proactive outreach program to fulfil the Commonwealth Government's duty of care towards those veterans.

Mefloquine and its Neurotoxic Side Effects

Mefloquine was discovered and developed by the US military during the 1970s, mainly in response to the onset of chloroquine-resistant falciparum malaria in Southeast Asia, and its ongoing development has been inextricably linked to military requirements and operations since that time.[7] First trialled in populations of US prisoners in the mid-1970s,[8] the drug has been used primarily for malaria chemoprophylaxis, with one of its perceived advantages over alternative drugs being that it can be taken as a weekly dose, rather than daily as is the case with doxycycline.[9] Military health officials believe that this leads to higher levels of "compliance" with the drug regimen and therefore greater effectiveness in preventing malaria than alternative drugs such as doxycycline.[10] Several authors have criticised the failure of regulatory processes in the US and Europe, including an absence of the necessary pre-licensing research, which might otherwise have prevented widespread harm caused by mefloquine's adverse side effects.[11]

The neuropsychiatric side effects of mefloquine have long been acknowledged by the manufacturer. Psychiatric side effects include, commonly – sleep disorders (insomnia, abnormal dreams); uncommonly – anxiety, depression, mood changes, panic attacks, confusion, agitation or restlessness, forgetfulness, hallucinations, aggression and psychotic or paranoid reactions; and rarely – suicidal ideation. Neurological side effects include, commonly – dizziness, loss of balance, headache, somnolence; uncommonly – sensory and motor neuropathies (including paraesthesia, tremor and ataxia), convulsions, syncope, and memory impairment; and rarely – encephalopathy.[12] Until recently, however, manufacturer's warnings and health

management policies have reflected the view that any such side effects can only be temporary, ceasing as the drug is eliminated from the body via the liver.[13]

This view has now been discredited in published scientific-medical research by Dr Remington Nevin, an epidemiologist at Johns Hopkins University, who has shown that mefloquine's neurotoxic side effects can in fact be long term or even permanent. Tracing the developmental history of mefloquine and other quinolines, Nevin finds that many of the above neurological side effects are consistent with the chronic sequelae[14] of a well characterised central nervous system (CNS) toxicity syndrome common to a number of quinolines and associated with *a risk of permanent neuronal degeneration* within specific CNS regions including the brainstem and emotional centres in the limbic system.[15] Further, Nevin discredits influential authors' previous attribution of the adverse side effects to the stress of travel, pre-existing mental illness, or "media hype."[16] At the very least, Nevin has established a plausible hypothesis for a causal relationship between mefloquine use and long term or permanent neurological side effects.

There is also substantial evidence of long term or permanent psychiatric side effects, dating back well over a decade. In 2000 for example, Danish and Swedish academics conducted follow-up research on mefloquine adverse event reports submitted to the Danish National Drug Authority from 1996 to 2000. Of 95 adverse event reports submitted during that period, they were able to evaluate acute and long term side effects in 76, or 89 per cent, of the 85 eligible, original subjects. In addition to their findings in relation to acute side effects, they found that those who had submitted adverse event reports during that period had "significantly poorer" standards of long term mental health, using standard psychiatric measures, compared to control groups matched by age and gender.[17]

Research findings such as these into mefloquine's long term or permanent neuropsychiatric side effects were reflected by the US Food and Drug Administration (FDA) in August 2013, when it mandated the most serious "black box" warning on mefloquine product labelling and issued the following public warning:

> *The US FDA is advising the public about strengthened and updated warnings regarding neurologic and psychiatric side effects associated with the antimalarial drug mefloquine hydrochloride. A boxed warning, the most serious kind of warning about these potential problems, has been added to the drug label. FDA has revised the [product labelling] to include this information and the possibility that the neurologic side effects may persist or become permanent. The neurologic side effects can include dizziness, loss of balance, or ringing in the ears. The psychiatric side effects can include feeling anxious, mistrustful, depressed, or having hallucinations.*[18]

Similar changes to mefloquine product labelling have also been mandated by the European drug regulators.[19] However the possibility of long term or permanent neuropsychiatric side effects associated with mefloquine use is yet to be reflected in Australia by either the manufacturer or the Therapeutic Goods Administration (TGA).[20] Even in the absence of local warnings, the US and European product warnings alone should cause concern by the ADF and DVA given that the drug and its side effects are the same regardless of the market in which it is sold.

Compounding the Problems of Veterans' Mental Health

Mefloquine and its neuropsychiatric side effects came to public notoriety when it was implicated in a cluster of murder-suicides in the early 2000s involving US veterans who had returned home from Iraq having taken the drug during their operational tours. Within a period of six weeks in mid-2002 three US soldiers from Fort Bragg killed their wives, two of whom then suicided, having recently returned from Afghanistan and taken mefloquine.[21] A 2007 literature review showed that mefloquine had already been causally associated with at least 19 deaths in users, including three suicides.[22] More recently it has been implicated in serious war crimes including the case of Robert Bales, who took mefloquine during his deployment to Iraq in 2003-04, before murdering 16 civilians in Afghanistan eight years later.[23] Further, the drug is drawing increasing attention in forensic psychiatry as its severe psychiatric side effects are being presented as defence or mitigating factors in criminal cases.[24]

Despite sustained criticism for its ostensibly short term psychotic side effects, mefloquine remained the anti-malarial drug of choice in the US military until 2009, when policies were introduced to restrict its use to personnel intolerant of alternatives such as doxycycline, as is the current ADF policy.[25] Even before the above research regarding a link between the drug and long term or permanent side effects however, Nevin and others were raising concerns about the compounding health impacts on veterans of Iraq and Afghanistan. Many troops who have returned from Iraq and Afghanistan experiencing mefloquine's neuropsychiatric symptoms, argues Nevin, have struggled to understand their symptoms and many have been misdiagnosed with PTSD or TBI. He further argues that some of those who did not experience the concussions or traumatic experiences that would explain their conditions have been accused of malingering, been discharged, or in some cases even suicided. [26] The US Center for Disease Control's *Health Information for International Travel* states explicitly that mefloquine's "neuropsychiatric side effects may confound the diagnosis and management of PTSD and TBI".[27] Nevin goes as far as saying that mefloquine neurotoxicity should be regarded as the "third signature injury of modern war", alongside PTSD and TBI.[28]

A useful case study on the impact of mefloquine on veterans' mental health involves the incidence of suicide among Irish peacekeeping veterans. In early 2013 Nevin analysed data from an investigation of suicides in the Irish Defence Force by television broadcaster RTÉ. Of the total number of Irish troops who had served on overseas peacekeeping deployments since the year 2000, 4,293 had taken mefloquine while 6,444 had not. Of the group who had taken mefloquine nine had suicided, while only four had suicided from the group who had not.[29] In Nevin's analysis, "troops prescribed mefloquine had a three to five fold increase in their risk of suicide in the years following deployment, as compared to similar troops deployed but not prescribed mefloquine."[30] An independent analysis of the same figures by Professor Simon Wilson, Head of Statistics at Trinity College Dublin, reached the same conclusion that the rate of suicides among those who took mefloquine was significantly higher than in those who did not.[31] Shortly after this investigation went to air, the manufacturer updated its local product information to warn that mefloquine could "cause suicide, suicidal thoughts and self-endangering behaviour."[32]

Some overseas military and veterans' health authorities are, however, beginning to respond to the problem of mefloquine neurotoxicity. Soon after the 2013 FDA "black bock warning quoted above, US Army Special Operations Command ordered that mefloquine no longer be used "due to risk of serious psychiatric and nerve side effects" and those exhibiting the symptoms undergo thorough medical assessment.[33] The US Department of Veterans Affairs (VA) lists mefloquine on documents advising veterans of "deployment exposures."[34] The VA War Related Injury and Illness Study Centre (WRIISC) has also commenced a clinical intake of veterans afflicted by mefloquine neurotoxicity.[35]

Possibly because of the smaller size of the ADF and its relatively long-standing policies restricting mefloquine use to those intolerant of doxycycline, the drug and its potential impact on veterans' mental health appears to have received scant attention in Australia. Given the published concerns over its long term neuropsychiatric side effects and compounding impact on veterans' mental health, re-examining its use within the ADF is now timely.

Mefloquine Use and Australian Veterans' Mental Health

Mefloquine was introduced into the ADF inventory as malaria prophylaxis in 1990[36] and has since been administered to personnel on major deployments including Somalia, Cambodia,[37] Bougainville, East Timor, Solomon Islands, Iraq and Afghanistan, as well as many other smaller operational and training deployments to malarious areas. Given the size and/or duration of those operations and anecdotal evidence of the widespread intolerability of alternatives such as doxycycline, a reasonable estimate of the number of ADF veterans who have had significant exposures to mefloquine neurotoxicity would be at least several thousand, possibly much higher. The drug remains in the ADF inventory for this purpose, but is not administered to divers, aircrew or joint battlefield airspace controllers because of "the possibility of severe central nervous system adverse effects."[38] Current ADF policy also states that "Due to the wide-spread public perception of severe mefloquine adverse events, mefloquine is best used only by those who have previously tolerated the medication."[39]

Prior to the current restrictive ADF policies however, in one case alone, 1,157 ADF personnel were administered mefloquine during 2001-02 drug trials by the Army Malaria Institute (AMI) in East Timor. During these trials there were nine reported "serious adverse events" among those who took mefloquine, including three participants who were withdrawn after experiencing "adverse events of a neuropsychiatric nature". One of these three soldiers "experienced depression, episodic anxiety, mild paranoia, short-term memory loss and suicidal ideation" and, despite being taken off mefloquine, his "mental state continued to deteriorate." There were anecdotal reports of many more adverse events, while "fifty-seven per cent of soldiers using mefloquine prophylaxis reported at least one adverse event," with the most commonly reported adverse effects being "sleep disturbance, headache, tiredness and nausea."[40] Following these trials there were numerous media reports that participants had experienced paranoia, suicide ideation and other psychotic side effects. One soldier was reported to have taken his girlfriend hostage at gunpoint soon after his return from East Timor.[41] The experiences of these participants are consistent with mefloquine's accepted neuropsychiatric side effects.

Notwithstanding the incidence of adverse side effects during or immediately after those trials, there are a number of legal, ethical and logical factors that now have renewed significance. Firstly, some of the participants reported that they were coerced or even bullied into taking mefloquine, which, coupled with the strong disincentive of being prematurely returned to Australia were they to report serious adverse psychotic events, make it reasonable to deduce that many more such events are likely to have gone unreported.[42] Secondly, a critical read of the trial reports shows that at least some reports of adverse side effects were likely to have been disregarded due to confirmation bias. Thirdly, 250 of the participants subsequently participated in a civil class action against the ADF and the manufacturers which was discontinued because the complainants would have been required to concede veterans' entitlements under the relevant legislation.[43] Given that the scientific consensus at the time was that mefloquine's neuropsychiatric side effects could only be temporary, the recent finding that they can in fact be long term or permanent potentially re-opens that legal case against the ADF, involving drug trials that may have been conducted unethically, for a drug that is now of questionable utility given the availability of alternative anti-malarial drugs such as malerone.

Without the necessary baseline investigations proposed below, it is not yet possible to make detailed estimates on how many Australian veterans have been affected by mefloquine neurotoxicity or the overall impact on veterans' mental health. However the likelihood that at least several thousand ADF personnel have taken mefloquine during their service since 1990, coupled with relevant outcomes from the multitude of recent ADF and veterans' mental health studies, does provide sufficient insight warrant further investigation. According to the *2010 ADF Mental Health Prevalence and Wellbeing Study*, of the population of just over 50,000 regular ADF personnel in 2010, with a mean length of service of 11.6 years, an estimated 43 per cent (or 21,500) had experienced multiple overseas operational deployments,[44] a large proportion of which would have included deployments to malarious areas where mefloquine was in use. In that year, 22 per cent of the ADF population experienced mental health disorders, including anxiety disorders such as PTSD and/or affective disorders such as depression. The prevalence of suicide ideation was "significantly higher in the ADF compared to the community", although the report does emphasise that ADF members were less likely to complete the act of suicide. Significantly, only half the sample with PTSD or depressive episodes reported receiving treatment in the previous 12 months, due to a variety of stigma.[45]

Even before the above health studies, Professor David Dunt conducted the 2009 *Independent Study into Suicide in the Ex-Service Community*. A weakness of this study is that it did not examine the role of prescription drugs as a causal factor, even though it did so in relation to illicit drug abuse, and discussed the role of prescription anti-depressants in suicide prevention. More broadly an important section of this study focused on the difficulties experienced by ADF personnel transitioning into civilian life for reasons of mental health and the possibility of negative reactions, some of which may lead to suicide. [46] This would tend to reinforce the argument that the relevant agencies should now be reaching out to veterans who may be suffering from mefloquine neurotoxicity and remain at risk of suicide.

Despite the sheer extent and cost of these studies, including analysis of factors such as trauma exposure, caffeine and tobacco use, alcohol and illicit drug abuse, even use of dietary supplements in relation to veterans' health, scant if any regard has been given to prescription drugs. Given that the ADF health authorities have been publicly dismissive of causal links between veterans' operational experiences and the incidence of mental health disorders or suicide, it would be ironic to say the least if they have simply overlooked what may prove to be one of the key causes, i.e. a known neurotoxic drug administered to many veterans during their ADF operational service. Mefloquine, a neurotoxic anti-malarial drug known for its neuropsychiatric side effects, which received widespread international media attention during this period, has become a prominent "blind spot", possibly even a case of wilful ignorance.

Anecdotally, this author is aware of at least several dozen serving or former ADF personnel who have taken mefloquine during operational service, experienced at least short term side effects, and have subsequently suffered from long term mental health problems. At the time of writing, few if any were aware of Nevin's research indicating that the side effects can be long term or permanent. Consistent with Nevin's concerns, at least several of those believe that they have been misdiagnosed with psychiatric disorders such as PTSD without having experienced the trauma that would support such diagnosis, or long term neurological conditions such as dizziness, balance problems, vertigo or tinnitus. This clearly warrants further investigation.

Recent reforms to the ADF and DVA mental health systems do provide a solid basis from which to develop a coordinated outreach program for those affected by mefloquine neurotoxicity. The 2009 *Dunt Review of Mental Health Care in the ADF and Transition through Discharge* recommended a series of reforms, including improved governance and policy, improved training, enhanced rehabilitation and transition services, and greater involvement of families.[47] Notably, the subsequent *2011 ADF Mental Health and Wellbeing Strategy* emphases the ADF's commitment to "evidence-based treatment and recovery programs" and "innovation and research that improves our understanding of mental health and wellbeing", through key objectives such as "identification and response to the mental health risks of military service" and "building an evidence base about military mental health and wellbeing".[48] For its part, the 2013 DVA *Veteran Mental Health Strategy* includes similar objectives, such as "strengthening workforce capacity" and "building the evidence base".[49] There is now a compelling case to initiate evidence-based treatment and recovery programs for veterans affected by mefloquine neurotoxicity, including a proactive outreach program to address ignorance of the problem across the health care system and among veterans themselves.

The Case for Proactive Outreach

The Commonwealth Government, including agencies such as the ADF and DVA, has a primary duty of care to veterans who have been administered mefloquine during their military service, whether those veterans remain serving members of the ADF or are now, or should be, under the care of DVA. The *Commonwealth Work Health and Safety (WHS) Act 2011* sets out a number of specific duties relevant to this case. Firstly, the ADF must ensure, as far as is reasonably practicable, the health and safety of serving personnel.[50] Secondly, it must ensure the provision and maintenance of a

work environment without risks to health and safety.[51] Thirdly, both the ADF and DVA must ensure the provision of any information, training, instruction or supervision that is necessary to protect all persons from risks to their health and safety arising from their service.[52] Finally, they must ensure that the health of personnel and the conditions at the workplace are monitored for the purpose of preventing illness or injury of personnel arising from the conduct of their service.[53] Given the above research on the long term or permanent mefloquine neurotoxic side effects, the ADF and DVA have clear legal obligations not only to prevent service personnel from further undue exposure, but to reach out to all currently serving and former ADF personnel who have taken mefloquine, in order to properly inform them of the new research findings, actively monitor their health and prevent further harm.

A parallel can be drawn with the recent ADF and DVA response to serious health problems experienced by RAAF maintenance personnel involved in the F-111 fuel tank "deseal/reseal" program. Over the period from 1977 to 1999, more than 400 personnel were directly exposed to toxic chemicals during their work maintaining F-111 aircraft, experiencing serious health problems as a result. The Commonwealth response involved a RAAF Board of Inquiry that identified numerous systemic shortcomings the chain of command and ADF health system, multiple health and toxicology studies involving RAAF personnel and their families, a Parliamentary inquiry and a $55 million compensation package. This process took almost a decade, causing significant reputational damage to the ADF.[54] Hypothetically, if a board of inquiry was conducted today into mefloquine use, the resulting neurotoxic side effects and their impact on the health of veterans of recent conflicts, findings similar to those made by the F111 Deseal/Reseal Board of Inquiry would likely be made regarding the shortcomings of the ADF health system, incident and hazard reporting and limitations of the chain of command in addressing systemic health threats such as those posed by mefloquine neurotoxicity. On the other hand, the experience of the F-111 deseal/reseal case, coupled with the post Dunt Review reforms, provides an opportunity for the Commonwealth to get things right.

Notwithstanding the outcomes of the Dunt Review and subsequent reforms to the ADF health system, several institutional barriers will need to be overcome in order to initiate a comprehensive response. For example the current ADF policy on mefloquine use still attributes concerns over mefloquine side effects to "public perception" rather than scientific evidence,[55] similar to the "media hype" cited by other influential authors now discredited by Nevin *et. al.* in published medical-scientific research. Further, SGADF and others have been publicly dismissive of any causal link between ADF operational service and mental health problems or suicide among veterans.[56] Given that a causal link may now be established between serious, long term mental health problems experienced by veterans, including the possibility of suicide, and an anti-malarial drug that was administered to them during their service, progressing this issue quickly and effectively from a *perception management* problem to a *veterans' health* problem will require strong leadership and good communication from the outset by senior ADF and DVA leaders.

Proposed Outreach Program

Given the absence to date of any coordinated response to the exposure of thousands of current and former ADF personnel to a neurotoxic drug which, at the very least has

contributed to the long term mental health problems of many veterans, the necessary response may well be initiated by Comcare, the Commonwealth Government's work health and safety authority. Comcare's functions and powers under the *WHS Act 2011* are extensive, including monitoring and enforcing compliance with the Act, providing advice and information to duty holders and the public, promoting and supporting education and training, and co-ordinating information sharing.[57] Comcare could play a key role in overcoming some of the institutional barriers and systemic weaknesses within the ADF hierarchy that have led to the current situation.

Notwithstanding any involvement from Comcare, the ADF can and should take the leading role in executing a thorough, timely response to this problem. Firstly, it should quickly investigate who and/or how many personnel were administered mefloquine during their service, as a baseline for a coordinated inter-departmental response. For serving personnel who have taken mefloquine, the ADF should then execute a comprehensive outreach program including awareness and education, training health staff, diagnosis, treatment and rehabilitation of affected personnel. A priority for the ADF concurrent with these activities should also be to initiate a research program on mefloquine neurotoxicity and its impact on veterans' mental health, with resources at least commensurate with those afforded to the various other health studies cited above.

The role for DVA in this response will be similar in many ways to that of the ADF, though obviously for ex-ADF members. Once the ADF has established the baseline of who and/or how many personnel were administered mefloquine during their service, DVA should execute a similar outreach program involving awareness, training, monitoring and treatment of veterans who can or should be under its care. Concurrently, one of the key activities that should be undertaken is for the Repatriation Medical Authority (RMA) to investigate the CNS toxicity syndrome identified by Nevin in order to develop the appropriate Statement of Principles (SOP) for those affected by mefloquine, in accordance with the *Veterans Entitlements Act 1986* (VEA) and the *Military Rehabilitation and Compensation Act 2004* (MRCA).[58] Nevin's most recent paper and related research clearly satisfies the requirement for "sound medical-scientific evidence" that satisfies the "reasonable hypothesis" standard of proof for this condition to be recognised as a disease and/or injury under the VEA and MRCA. [59] The timely development of an SOP by the RMA would facilitate recognition, rehabilitation and compensation for affected veterans, thereby preventing or alleviating additional stress that would otherwise compound their existing problems.

Conclusion

The case for a program of proactive outreach to veterans affected by the neurotoxic side effects of mefloquine during their ADF service is compelling, consistent with the ADF's evidence-based approach to mental health, as well as the ADF and DVA's primary duty of care under the *WHS Act 2011*. The fact that mefloquine is a neurotoxic drug that can cause neuropsychiatric side effects is not disputed by the manufacturer, relevant health authorities, or the ADF. The only area of dispute has been whether the side effects are only temporary, or can be long term or permanent. There is now strong evidence that the side effects can be long term or permanent, leading the US FDA and other regulators to mandate drug labelling to that effect.

Further, mefloquine was administered to a significant proportion of the current wave of US, British and other veterans suffering from long term mental health problems including depression, anxiety and PTSD, indeed many of those may have been misdiagnosed and/or mistreated, resulting in further harm or risk. At least 1,157 ADF personnel were administered mefloquine during drug trials as part of their military service, 250 of whom subsequently took part in a civil class action after complaining about neuropsychiatric side effects, when the conventional wisdom was that these could only be temporary. The total number of ADF personnel who used the drug would be at least several thousand, although the actual figure could be much higher. Finally, there is anecdotal evidence that many Australian veterans who took mefloquine during their ADF service, then served in Iraq, Afghanistan and/or other conflicts, probably at least several hundred, have suffered from long term mental health problems that have been incorrectly attributed solely to their experiences in those conflicts rather than being caused at least in part by the neurotoxic side effects of mefloquine.

Overseas military and veterans' authorities have begun to implement programs to support affected veterans. The ADF and DVA need to respond accordingly. Failing to do so would not only place the health and wellbeing of veterans and their families at further risk, but also cause serious reputational damage to both organisations and ultimately incur far greater cost to the Commonwealth than timely, proactive intervention. Both organisations must now adopt a position of leadership in order to care for the affected veterans by implementing an outreach program along the lines of that proposed above. Indeed Australia *could* potentially take a leading role in what will likely become an international effort for affected veterans.

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Precedence: ROUTINE
DAC: General
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REF/C/DRUG SAFETY COMMUNICATION/FDA/29JUL2013// REF/D/DODI/DOD/20MAR2009//
REF/E/DOCUMENT/NCMI/23AUG2011
REF/F/ARTICLE/J AM ACAD PSYCHIATRY LAW/41:2013// NARR/REF A IS OSD-HA MEMORANDUM "GUIDANCE ON MEDICATIONS FOR PROPHYLAXIS OF MALARIA". REF B IS HA POLICY 09-017 "POLICY MEMORANDUM ON THE USE OF MEFLOQUINE (LARIUM) IN MALARIA PROPHYLAXIS". REF C IS FDA DRUG SAFETY COMMUNICATION "FDA APPROVES LABEL CHANGES FOR ANTIMALARIAL DRUG MEFLOQUINE HYDROCHLORIDE DUE TO RISK OF SERIOUS PSYCHIATRIC AND NERVE SIDE EFFECTS". REF D IS DODI 6420.01 NATIONAL CENTER FOR MEDICAL INTELLIGENCE. REF E IS DEFENSE INTELLIGENCE REFERENCE DOCUMENT DIA-16-1108-093 "USING NCMI MALARIA RISK ASSESSMENTS TO SUPPORT CHEMOPROPHYLAXIS CHOICES". REF F IS A PEER REVIEWED ARTICLE "PSYCHIATRIC SIDE EFFECTS OF MEFLOQUINE: APPLICATIONS TO FORENSIC PSYCHIATRY".// 1. (U) SITUATION. ON 29 JUL 2013 THE FDA ANNOUNCED A BLACK BOX WARNING FOR MEFLOQUINE IN A SIGNIFICANT CHANGE TO THE DRUG'S APPROVED LABELING. UPDATED FDA GUIDANCE NOW EXPANDS ON PRIOR GUIDANCE TO EMPHASIZE THE NEED TO DISCONTINUE MEFLOQUINE SHOULD ANY NEUROLOGICAL OR PSYCHIATRIC SYMPTOMS DEVELOP WHILE TAKING THE DRUG AND HIGHLIGHTS THAT CERTAIN NEUROLOGIC SYMPTOMS HAVE BEEN REPORTED TO BE PERMANENT. FURTHER, MILITARY AUTHORS WRITING FOR THE CDC HAVE NOTED THAT THE SYMPTOMS CAUSED BY MEFLOQUINE MAY "CONFOUND THE DIAGNOSIS" OF PTSD AND TBI. THE UPDATED PRODUCT DOCUMENTATION NOTES THAT PSYCHIATRIC SYMPTOMS RANGING FROM ANXIETY, FEELING RESTLESS OR CONFUSED, PARANOIA AND DEPRESSION TO

HALLUCINATIONS AND PSYCHOTIC BEHAVIOR CAN OCCUR AND CONTINUE FOR MONTHS OR YEARS AFTER MEFLOQUINE USE; CASES OF SUICIDAL IDEATION AND SUICIDE HAVE BEEN REPORTED.// 2. (U) MISSION. USASOC COMMANDERS AND MEDICAL PERSONNEL WILL DECREASE THE RISK OF NEGATIVE DRUG RELATED SIDE EFFECTS BY CEASING USE OF MEFLOQUINE AS A MEANS OF CHEMOPROPYLAXIS FOR THE PREVENTION OF MALARIA; CONCURRENTLY ADDRESS AND ASSESS THE POSSIBILITY AND IMPACT OF MEFLOQUINE TOXICITY IN THEIR POPULATIONS.// 3. (U) EXECUTION.
3.A. CONCEPT OF THE OPERATION.
3.A.1. USASOC MEDICAL PERSONNEL WILL IMMEDIATELY CEASE THE PRESCRIBING AND USE OF MEFLOQUINE FOR MALARIA PROPHYLAXIS.
3.A.2. PERSONNEL CURRENTLY TAKING MEFLOQUINE FOR PREVENTION OF MALARIA WILL TRANSITION TO ONE OF THREE ALTERNATIVE OPTIONS FOR PROPHYLAXIS DEPENDING ON THEIR LOCATION, DRUG RESISTANCE, AND THE MALARIA RISK.
3.A.3. PERSONNEL CONDUCTING MEDICAL INTELLIGENCE PREP OF THE ENVIRONMENT (MIPOE) WILL REVIEW REF E TO IDENTIFY PREVALENCE AND TYPE OF MALARIA AS WELL AS DRUG RESISTANCE TO ENSURE THE APPROPRIATE USE OF EFFECTIVE MEDICATIONS.
3.A.3.A. MEDICAL PERSONNEL WILL ENSURE THAT THE SELECTION OF ATOVAQUONE-PROGUANIL (MALARONE), DOXYCYCLINE OR CHLOROQUINE IS DRIVEN BY COMMAND POLICY, PREVALENCE AND TYPE OF MALARIA, INDIVIDUAL CONTRAINDICATIONS, AND REGIONALLY UNIQUE DRUG RESISTANCE.
3.A.3. PERSONNEL REDEPLOYING FROM P. VIVAX ENDEMIC AREAS (IAW REF E) WILL CONTINUE TO TAKE FOURTEEN DAYS OF APPROVED POST-EXPOSURE CHEMOPROPHYLAXIS (PRIMAQUINE).
3.A.4. MEDICAL PERSONNEL WILL ADDRESS AND, IF APPROPRIATE, REFER REPORTS OF SUSPECTED CASES OF "MEFLOQUINE TOXICITY" IAW COORDINATING INSTRUCTIONS.
3.B. COORDINATING INSTRUCTIONS.
3.B.1. COMMANDERS AND SUPERVISORS AT ALL LEVELS WILL:
3.B.1.A. ENSURE THAT DEPLOYED PERSONNEL CONTINUE TO BE PROTECTED FROM MALARIA THROUGH THE USE OF ATOVAQUONE-PROGUANIL, DOXYCYCLINE AND CHLOROQUINE (PRE-EXPOSURE) AND PRIMAQUINE (POST-EXPOSURE FOR P. VIVAX AND P. OVALE ENDEMIC AREAS) IAW COMMAND POLICY.
3.B.1.B. APPROVED MEDICATIONS FOR MALRIA CHEMOPROPHYLAXIS IN USASOC.
3.B.1.B.1 ATOVAQUONE-PROGUANIL IS THE FIRST LINE CHEMOPROPHYLAXIS FOR USASOC PERSONNEL BASED ON THE RESIDUAL PROTECTION AND MINIMAL SIDE-EFFECT PROFILE. DOXYCYCLINE IS AN EQUALLY EFFECTIVE MEDICATION FOR THE PREVENTION OF MALARIA AND NO KNOWN RESISTANCE EXISTS. IF EVIDENCE OF ATOVOQUONE-PROGUANIL RESISTANCE EXISTS OR EMERGES, DOXYCYCLINE IS THE DRUG OF CHOICE. PRE-DEPLOYMENT RESEARCH IS CRITICAL TO DETERMINING THE MOST APPROPRIATE AND EFFECTIVE CHEMOPROPHYLAXIS FOR ANY DEPLOYMENT.
3.B.1.B.2. THE EFFECTIVENESS OF CHLOROQUINE VARIES BY TYPE OF MALARIA AND BY REGION.
3.B.1.B.2.A. P. FALCIPARUM: HIGH LEVELS OF RESISTANCE RESULTING FROM YEARS OF HEAVY USE HAVE RENDERED CHLOROQUINE INEFFECTIVE IN THE PREVENTION OF P. FALCIPARUM MALARIA IN AFRICOM, CENTCOM, PACOM, AND A FEW AREAS OF SOUTHCOM. CHLOROQUINE REMAINS AN EFFECTIVE CHEMOPROPHYLAXIS AGAINST P. FALCIPARUM ONLY IN PARTS OF SOUTHCOM, INCLUDING BELIZE, COSTA RICA, THE DOMINICAN REPUBLIC, EL SALVADOR, HAITI, HONDURAS, NICARAGUA, AND PARAGUAY.
3.B.1.B.2.B. P. VIVAX: HIGH LEVELS OF CHLOROQUINE-RESISTANT P. VIVAX HAVE BEEN REPORTED IN TURKEY AND INDONESIA, AND RESISTANCE IS INCREASINGLY BEING DOCUMENTED THROUGHOUT MUCH OF ASIA. INCREASING RESISTANCE HAS BEEN NOTED IN PARTS OF SOUTHCOM, PARTICULARLY IN BRAZIL AND COLOMBIA. DESPITE MANY YEARS OF CHLOROQUINE

USE, EVEN AS SINGLE-DRUG THERAPY, CHLOROQUINE REMAINS LARGELY EFFECTIVE AGAINST P. VIVAX IN MUCH OF CENTCOM.
3.B.1.B.3. POST-EXPOSURE CHEMOPROPHYLAXIS WITH PRIMAQUINE IS NECESSARY TO KILL THE LIVER STAGE OF THE P. VIVAX AND P. OVALE MALARIA PARASITES. IF NOT TREATED WITH PRIMAQUINE THESE TYPES OF MALARIA WILL RELAPSE UNTIL THE LIVER STAGE OF THE PARASITE IS TREATED.
3.B.1.B.3.A. PRIMAQUINE IS NOT BE USED IN PERSONNEL WITH G6PD DEFICIENCY WITHOUT THE CONSULTATION OF AN INFECTIOUS DISEASE SPECIALIST.
3.C. MEFLOQUINE TOXICITY.
3.C.1. SEE ENCLOSURE 1 FOR DETAILS REGARDING THE SYMPTOMS OF MEFLOQUINE TOXICITY BASED ON ITS POSSIBLE EFFECTS ON THE LIMBIC SYSTEM AND BRAINSTEM.
3.C.2. CLINICAL EXPERTISE ON MEFLOQUINE TOXICITY IS CURRENTLY LIMITED; HOWEVER THERE ARE INDIVIDUAL CLINICIANS AVAILABLE FOR CONSULTATION.
3.C.2.A. CLINICAL QUERIES REGARDING MEFLOQUINE-RELATED VESTIBULAR DISORDERS MAY BE DIRECTED TO CAPT MICHAEL E. HOFFER, MC, NAVAL MEDICAL CENTER SAN DIEGO, MICHAEL.HOFFER@MED.NAVY.MIL, (619) 532-6964.
3.C.2.B. GENERAL CLINICAL INQUIRIES REGARDING SUSPECTED CASES OF MEFLOQUINE TOXICITY MAY BE SUBMITTED THROUGH THE WAR RELATED ILLNESS AND INJURY STUDY CENTER (WRIISC) WEBSITE: WWW.WARRELATEDILLNESS.VA.GOV.
3.C.3. PERSONNEL CURRENTLY IN OR TRANSITIONING TO THE VETERANS HEALTHCARE ADMINISTRATION (VHA) CAN BE REFERRED TO THE WRIISC BY A PROVIDER IN THE VHA. POC AT THE WRIISC IS DR. DREW HELMER, DREW.HELMER@VA.GOV, (908) 202-4382.
4. (U) SUSTAINMENT. N/A.//
5. (U) USASOC POCS.
5.A.1. SURGEON CHOPS IS LTC CURTIS DOUGLASS 910-432-3038 CURTIS.W.DOUGLASS@AHQB.SOC.MIL.
5.A.2. USASOC SURGEON POC IS COL JENNIFER CACI 910-432-9884 JENNIFER.CACI@AHQB.SOC.MIL.
AUTHENTICATION/BROWER, COL, COFS, OFFICIAL: DODGE, COL, G3//
AKNLDG/YES/INST: ALL CSC/U ACKNLDG UPON RECEIPT, TO DSN 236-0371, COMM (910) 396-0371.// ENCLOSURE 1. (U) INFORMATION PAPER: SIDE EFFECTS OF MEFLOQUINE.// BT UUUU

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AOMD
3 Sep 13

INFORMATION PAPER

SUBJECT: Side Effects of Mefloquine

1. Purpose. On 29 July 2013 the FDA announced a black box warning for mefloquine in a significant change to the drug's approved labeling. Updated FDA guidance now expands on prior guidance to emphasize the need to discontinue mefloquine should any neurological or psychiatric symptoms develop while taking the drug.

2. Summary. The development of any neurological or psychiatric symptoms may be an indication of a personal risk of mefloquine toxicity. These symptoms may occur at any time during use of mefloquine, even among individuals who have previously tolerated the drug. Recent changes in the product documentation warn of the potential for long lasting serious mental health problems and based on the widespread use of mefloquine within ARSOF consideration must be made for the impact of this medication on our population.

3. Background and Discussion.

a. Since 1989 mefloquine product labeling has warned that if symptoms of "anxiety, depression, restlessness or confusion" developed while taking the drug, the drug must be discontinued.

b. Some U.S. military personnel who were prescribed the drug despite a history of mental illness or TBI may have incorrectly attributed side-effects to their pre-existing condition, rather than to the drug. As a result, military personnel with persistent symptoms following use of mefloquine should be evaluated for the effects of possible drug toxicity.

d. The CDC now notes that the symptoms caused by mefloquine may "confound the diagnosis" of PTSD and TBI. Therefore lasting symptoms resembling those of PTSD or TBI without clear attribution to personal history need to be considered in the differential diagnosis.

e. Careful attention must also be paid to symptoms previously contributing to the diagnosis of malingering, conversion, somatoform, or personality disorders, as the subtle neurological and psychiatric effects of mefloquine toxicity may mimic or be mistaken for these disorders.

f. Neurologic symptoms such as dizziness or vertigo, tinnitus, and loss of balance have been reported. These adverse reactions may occur early in the course of mefloquine use and in some cases have been reported to continue for months or years after mefloquine has been stopped. Dizziness or vertigo, tinnitus and loss of balance have been reported to be permanent in some cases.

g. Psychiatric symptoms ranging from anxiety, paranoia and depression to hallucinations and psychotic behavior can occur with mefloquine use. Symptoms may occur early in the course of mefloquine use and in some cases these symptoms have been reported to continue for months or years after mefloquine has been stopped. Cases of suicidal ideation and suicide have been reported. The updated patient U.S. medication guide expands the list of psychiatric symptoms that can occur to include "feeling restless, unusual behavior or feeling confused".

h. Literature review suggests additional psychiatric symptoms may occur from the drug's toxicity, to include persistent sleep disorders and nightmares, cognitive problems, particularly deficits in short-term memory, panic attacks and agoraphobia, and changes in mood and personality, particularly irritability and decreased impulse control.

i. It is highly unlikely that individuals who have previously taken mefloquine without issue will suffer ill effects in the absence of future use.

j. There is limited support for clinical queries regarding mefloquine toxicity at this time. However, specific questions regarding mefloquine-related vestibular disorders may be directed to CAPT Michael E. Hoffer, MC, Naval Medical Center San Diego, michael.hoffer@med.navy.mil, office (619) 532-6964. General inquiries regarding suspected cases of mefloquine toxicity may be submitted through the War Related Illness and Injury Study Center (WRIISC) website: www.warrelatedillness.va.gov. The USASOC Surgeon's Office (910-432-9884) is also available to field queries and assist in finding clinical support.

COL J. CACI/910-432-9884